Morgan Lewis

LIFE SCIENCES
INTERNATIONAL REVIEW

Welcome to the Q1 2019 issue of our *Life Sciences International Review*. This issue covers life sciences developments within Europe, Asia, and the United States in the areas of Brexit, intellectual property, regulatory, and competition, to name a few.

As you will find, many of the subjects covered in this issue are ongoing. The *Life Sciences International Review* team continues to monitor developments and will include updates in future issues to keep our readers current with the latest events and trends in the life sciences industry.

Read the latest issue of *Life Sciences International Review* >

BREXIT

UK and EU Positions on Brexit 'No Deal' Planning for the Life Sciences Sector: Current State of Play

The ever-evolving Brexit saga is still continuing to unfold but, in the process, has left many open questions for regulated European Union (EU) and United Kingdom (UK) businesses, including those in the biopharmaceutical industry. While the risk of a no-deal exit is at least now averted until October 31, 2019, at the earliest, and is not a favored option, it is perceived as a continuing possibility and plans are in place to deal with this eventuality.

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UK Medicines Proposals

For medicines, the proposals include

- automatically converting Community Marketing Authorisations to UK Marketing Authorisations, a process known as "grandfathering";
- a targeted assessment of new applications for products containing new active substances or biosimilars that have been submitted to the European Medicines Agency (EMA) and received a Committee for Medicinal Products for Human Use (CHMP) positive opinion;
- a full accelerated assessment for new active substances;
- free scientific advice, including for orphan medicines, for UK-based small and medium-sized enterprises;
- a period until the end of 2021 to amend packaging and leaflets for products already on the market;
- allowing the parallel import of medicinal products that hold marketing authorisations from EU or EEA countries; and
- continuing to recognize prescriptions issued in EU or EEA countries.

This guidance is being updated on an ongoing basis and applies to specific types of products including human tissue and blood products. While confusion and the pace of events mean that any analysis and report will only ever be a snapshot on current developments, the MHRA has **current plans** on how the sector should respond if the UK does leave without a deal.

In addition, the UK NHS Health Research Authority (HRA) **proposals** address specific research issues including a commitment to cover already-granted EU research grants until the end of 2020. For clinical trials, the plans include

- continuing to recognize existing approvals so there will be no need to reapply;
- requiring the sponsor or legal representative of a clinical trial to be in the UK or a country on an approved country list that would initially include EU or EEA countries; and
- aligning, where possible, with the EU Clinical Trials Regulation when it applies.

UK Medical Devices Proposals

For medical devices, the key arrangements include

- for a limited period, devices that have a CE mark from a notified body based in the UK or an EU country will continue to be recognized by UK law and allowed to be placed on the UK market; and
- the expansion of the MHRA's registration system to all classes of medical devices (currently only Class 1 is covered).

These proposals are similarly being continually updated. Also read this broader **life sciences industry Brexit impact review** from the Department for Business, Energy and Industrial Strategy.

UK IP Proposals

In addition, the UK Department for Exiting the EU has issued **guidance on continuity** in relation to patents and supplementary protection certificates after Brexit.

EU Medicinal Product Guidance

In addition, on February 1 the European Commission issued a **revised and updated Q&A** list related to the United Kingdom's withdrawal from the European Union with regard to medicinal products for human and veterinary use within the framework of the Centralised Procedure. New issues raised include the conclusion that parallel trade into the EU of medicines sourced in the UK would in practice no longer be possible after the withdrawal date, and the consequences under the Falsified Medicines Directive of the UK withdrawal. For more, see the European Medicines Agency's **current advice page** with this and other guidance for producers of medicinal products.

EU Medical Device Guidance

See **guidance applicable to CE-marked producers** generally but including medical devices and a **Q&A paper** that includes such topics as what is meant by "placing on the market" in order to know what individual products can be legally distributed and used in the EU after Brexit.

EU Cosmetics Guidance

In relation to cosmetics, there is a requirement under the EU Cosmetics Regulation that cosmetic products be placed on the single market only through designated "responsible persons" established in the European Union. Once the United Kingdom leaves, established responsible persons in Britain will need to transfer their roles to either importers or other responsible persons set up in the EU. Another significant change concerns the obligation to notify product information through the Cosmetics Product Notification Portal. UK manufacturers and traders will no longer be able use the portal directly, but will need to rely on EU entities to do it for them. See **guidance** on these and other related changes.

Impact on the EMA

For the EU, the EMA's move from London to Amsterdam has been hugely disruptive, due to both staff departures and the reallocation of 30% or more of the tasks within the EMA performed by the MHRA to other, arguably less experienced, member states, and has resulted in a significant reduction in the nonessential work of the agency. In late January, the EMA published an **updated list of priorities** from its work program. In the short term, the EMA's main focus will be on

- the authorisation, maintenance, and supervision of medicinal products;
- ongoing Brexit preparedness and implementation activities; and

- preparing for the implementation of the new veterinary legislation.

The EMA has moved into temporary headquarters at the Spark building in Amsterdam, and in a recent twist, the UK High Court ruled that the EMA's 25-year lease for its London headquarters with the Canary Wharf Group will not be discharged by frustration on the United Kingdom's transition from the European Union, nor does the EMA's shift of headquarters from London to Amsterdam constitute a frustrating event. Therefore the EMA remains obligated to fulfill its lease obligations.

Summary

The whole process of departure has been difficult and divisive for the United Kingdom, and frustrating for the other member states due to a lack of a clear UK voice, largely as a result of vacillating leadership of the two main parties. At the time of writing, nearly three years since the exit referendum, no one has much of an idea on the UK's final destination. For the life sciences sector, almost entirely regulated under EU laws, the immediate trauma of leaving without a deal is likely to be severe.

The EMA predicts that Brexit-related costs in 2019 will amount to €45 million, which includes staff relocation, removal, archiving, and legal and consultancy costs.

INTELLECTUAL PROPERTY

In Split Decision, Federal Circuit Invalidates Diagnostic Method Patent

A split panel of the US Court of Appeals for the Federal Circuit held on February 6 that claims to an assay for diagnosing myasthenia gravis are not patent eligible because they are directed to a natural law. The majority decision in *Athena Diagnostics v. Mayo Collaborative Services* is in line with a series of decisions by the Federal Circuit in which diagnostic method claims were found to be not patent eligible.

Athena is the exclusive licensee of US Patent No. 7,267,820, which is based upon the discovery that autoantibodies to the MuSK protein cause myasthenia gravis. The '820 patent claims methods for diagnosing myasthenia gravis by detecting MuSK autoantibodies. Claim 9 of the '820 patent describes a specific test for MuSK autoantibodies using a radioimmunoassay, and was the most specific claim considered by the court. According to claim 9, MuSK is radioactively labeled with Iodine-125, a radioactive isotope of Iodine, and then contacted with a bodily fluid. If the bodily fluid contains MuSK autoantibodies, the autoantibodies and Iodine-125-labeled protein will form immune complexes. The immune complexes are collected and then monitored for the presence of the radioactive label, which indicates a diagnosis of myasthenia gravis.

Patent eligibility is analyzed under a two-step test set forth by the US Supreme Court in *Mayo* and *Alice*. The first step is to determine whether the claims are directed to a natural law, abstract idea, or other patent-ineligible subject matter. The second step asks whether the claims contain an inventive concept that transforms the claims into a patent-eligible application of the underlying ineligible subject matter. The majority opinion authored by Judge Alan Lourie focused on claim 9 as it was the most specific one at issue. In the first step, the majority identified "the correlation between the presence of naturally-occurring MuSK autoantibodies in bodily fluid and MuSK related neurological diseases like [myasthenia gravis]" as a natural law because it "exists in nature apart from any human action." The majority determined that the claims are "directed to a natural law because the claimed advance was only in the discovery of a natural law, and that the additional recited steps only apply conventional techniques to detect that natural law." In the second step, the majority recognized that the additional steps did not represent "an inventive application beyond the discovery of the natural law itself" because the patent itself described the detection steps as standard techniques in the art.

Judge Pauline Newman dissented. In her view, the majority's analysis of patent eligibility was incorrect because the court should have considered the claims as a whole, including all their elements and limitations. Judge Newman concluded that viewed as such, the claims are for a novel multistep method of diagnosis, not a law of nature. In Judge Newman's opinion, it was incorrect for the majority to separate the claim steps according to whether they are performed using conventional techniques, and then to ignore the presence of the conventional steps in the analysis. Section 101 does not turn on whether any claim steps are "standard techniques," according to Judge Newman. "The appropriate analysis of the role of conventional steps in claims to a new method is under Sections 102 and 103, not Section 101."

The split decision in *Athena* reflects competing views on the application of the *Mayo* test to diagnostic method claims, but the outcome of the case is patent ineligibility in yet another diagnostic method case.

Read the full **LawFlash**.

Earlier Blocking Patent Discounts Evidence of Secondary Considerations

Acorda Therapeutics, Inc. v. Roxane Labs., Inc.
(Fed. Cir. Sept. 10, 2018)

The US Court of Appeals for the Federal Circuit affirmed the district court's finding that Acorda's patents for the use of extended-release formulations of 4-aminopyridine (4-AP) to treat patients suffering from multiple sclerosis (MS) were obvious in view of the prior art. The court discounted the weight of the alleged secondary considerations (e.g., commercial success, failure of others, and long-felt but unmet need) due to an earlier blocking patent. *Acorda*

Therapeutics, Inc. v. Roxane Labs., Inc., 2017-2078, 2017-2134 (Fed. Cir. Sept. 10, 2018) (Taranto, J.).

In 1997, Acorda licensed a patent from Elan that broadly claimed a method of treating MS by administering a sustained-release formulation containing 4-aminopyridine (4-AP). Shortly thereafter, Acorda began investigating the use of 4-AP to treat MS and conducted studies that resulted in Acorda filing and obtaining its own patents directed to (1) a 10 mg dose of 4-AP administered twice daily; (2) a stable sustained-release formulation of 4-AP; (3) dosing to achieve 15-35 ng/mL serum levels of 4-AP; and (4) improved walking in MS patients. The broader Elan patent and the more specific Acorda patents were Orange Book–listed for Acorda's Ampyra®, a 10 mg 4-AP sustained-release tablets for twice daily administration.

The defendants, Roxane Laboratories, Mylan Pharmaceuticals, and Teva Pharmaceuticals USA, submitted Abbreviated New Drug Applications (ANDAs) seeking approval to market generic versions of Ampyra. In July 2014, Acorda sued the defendants in the Delaware district court alleging infringement of claims in each of the Elan and Acorda patents. At trial, the defendants stipulated to infringement but challenged the validity of the asserted claims. The district court held the asserted claims in the Acorda patents invalid for obviousness, but the court upheld the validity of the asserted Elan patent claims and enjoined the defendants until the Elan patent expired on July 30, 2018.

The defendants' cross-appeal of the district court's ruling that the Elan patent was not invalid was dismissed as moot because the Elan patent had expired and no respective liability was at issue.

To read more about this matter, please see the Morgan Lewis publication, ***Pharma Review***.

Residency of a Nonparty May Be Imputed to Defendant Where Entities Take On an Alter Ego Relationship

Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc. (D. Del. Oct. 18, 2018)

Addressing whether residency of one entity can be imputed to another for purposes of the patent venue statute, the US District Court for the District of Delaware held that residency can be imputed for purposes of satisfying the first prong of 28 U.S.C. § 1400(b), but that Bristol-Myers Squibb Company (BMS) failed to meet the heavy burden of proving an alter ego relationship between defendant Mylan Pharmaceuticals Inc. (MPI) and its wholly owned Delaware subsidiary, Mylan Securitization LLC. Separately, Judge Stark held that patent infringement cases arising under the Hatch-Waxman Act are governed solely and exclusively by Section 1400(b), not Section 1391. *Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc.,* Case Nos. 17-374, -379 (D. Del. Oct. 18, 2018) (Stark, C.J.).

MPI, incorporated in West Virginia, filed a motion to dismiss for improper venue based on the US Supreme Court's *TC Heartland* decision. MPI argued that it is not incorporated in Delaware, did not perform the alleged act of infringement in Delaware, and does not maintain a regular and established place of business in Delaware. In addition, MPI argued that the residency of a nonparty affiliate, Mylan Securitization, should not be imputed to it based on the common law doctrines of "alter ego" and "piercing the corporate veil." Finally, MPI argued that even if these common law doctrines applied, BMS failed to meets its burden of proof.

BMS argued that the Delaware residency of Mylan Securitization should be imputed to MPI due to an alter ego relationship between the two entities. BMS only argued for proper venue under the first prong of Section 1400(b) (i.e., residency), and not the second prong (i.e., acts of infringement and regular and established place of business) because there was insufficient discovery on the second prong. BMS asserted an alter ego relationship based on Mylan Securitization (1) being a wholly owned subsidiary of MPI; (2) having none of its own employees, revenue, profits, or facilities; (3) being represented by the same lawyers in transactions with MPI; (4) having minimal costs of operation; and (5) sharing an overlapping director with MPI. BMS alternatively argued that in the Hatch-Waxman context, venue should be governed by Section 1391, not Section 1400(b), and under Section 1391, there is no dispute that venue was proper in Delaware.

Turning first to the question of whether residency may be imputed under the first prong of Section 1400(b), the court agreed with BMS, but determined that BMS failed to meet its heavy burden and dismissed each of BMS's arguments in turn. The court found that BMS failed to produce any evidence showing corporate formalities were ignored or anything improper or illegal occurred when creating Mylan Securitization. The court found that there was nothing improper about creating a wholly owned LLC for tax purposes; there was no evidence of undercapitalization or insolvency of MPI based on its relationship with Mylan Securitization; and the structure of the MPI and Mylan Securitization was for the legal purpose of increasing the amount of cash to MPI. It also found that using the same lawyers in a transaction was not improper because the transactions were not secret and there was no evidence of a sham or fraudulent negotiation. Finally, the court found no fault in sharing one overlapping director, which did not show that corporate formalities were ignored. Most importantly, the court found that BMS failed to show any evidence of fraud, unfairness, or injustice. Accordingly, the court refused to impute MPI with the residency of Mylan Securitization, and dismissed the case for improper venue.

The court also dispensed with BMS's alternative argument, that Hatch-Waxman patent infringement cases should be governed by Section 1391, not Section 1400(b). The court held that because Hatch-Waxman cases arise out of the

patent statute, and the 30-month stay of generic approval is triggered by bringing a patent infringement action, Hatch-Waxman litigation is incontestably an action for patent infringement governed solely and exclusively by Section 1400(b).

To read more about this matter, please see the Morgan Lewis publication, ***Pharma Review***.

REGULATORY

What's in a Name? FDA Proposes Updates to Its Biosimilar Naming Policy

The US Food and Drug Administration (FDA) issued an updated draft guidance on March 7 on the nonproprietary naming of biologics, titled Nonproprietary Naming of Biological Products: Update (Guidance). This update is FDA's second attempt at guidance concerning nonproprietary name suffixes for biologic products. It also highlights the perceived tension between FDA's pharmacovigilance role and goal of increasing the availability of biosimilars. At least for this round, FDA's interest in tracking pharmacovigilance data seems to have received priority.

Through the updated Guidance, FDA announced four key changes to its approach to biologic product nonproprietary name suffixes.

First, FDA stated that it will not modify the nonproprietary names of biologics that have already been licensed without a designated suffix. FDA Commissioner Dr. Scott Gottlieb stated in a press release accompanying the Guidance that this particular change was in response to concerns from stakeholders that retroactive name changes would impose substantial costs on the healthcare system and could cause confusion in the market. In view of these potential issues, FDA determined that the agency's pharmacovigilance goals could be accomplished without extending the new naming convention to already licensed products.

Second, along the same vein, FDA will not apply the new naming convention to transition biologics. These products are biologics, such as insulin, that are currently approved under New Drug Applications (NDAs) rather than Biologic License Applications (BLAs). In March 2020, however, these existing NDAs will be converted to BLAs. According to the press release, this step is to minimize burden, ensure patient stability, and advance the development of biosimilar and interchangeable products.

Third, interchangeable biosimilars will have a designated proper name like that of non-interchangeable biosimilars, which will comprise a combination of a core name and a distinguishing suffix.

Fourth and finally, FDA is reconsidering whether vaccines, which are currently within the scope of FDA's biologic naming framework, should require suffixes, as currently available identification systems may meet FDA's pharmacovigilance goals.

From the Morgan Lewis blog, ***As Prescribed***.

New York's Drug Take Back Act Starts Slowly

The New York State Drug Take Back Act (Act), which was signed into law on July 10, 2018, went into effect on January 6. However, due to statutory timelines, enforcement actions are unlikely to start until after October 2019. Nonetheless, drug manufacturers should continue to diligently work toward the various Act deadlines, as development of a drug take-back program will require an investment of manufacturer time and money.

By way of background, the Act imposes significant requirements on drug manufacturers to develop, implement, and pay for a statewide drug take-back program covering most prescription and over-the-counter drugs, whether for use by humans or animals, including controlled substances (covered drugs). Manufacturers may operate a program in one of three ways. First, programs may be operated individually or jointly with other manufacturers, but the program must first be proposed to and approved by the New York State Department of Health (Department). In the alternative, manufacturers may enter into an agreement with a "drug take-back organization," and that organization can submit a proposal to the Department on behalf of the manufacturer or a group of manufacturers. The third statutory option is to enter into an agreement with the Department to operate a program on the manufacturer's behalf. The Department has not yet published any explanatory information on this third option. Program proposals must be submitted by July 5, 2019.

After receiving a manufacturer's program proposal (between now and July 5, 2019), the Department will review it within 60 days, consult with the New York State Department of Environmental Conservation to determine whether the program complies with the Act, and notify the applicant of approval or denial. Depending on when a manufacturer submits its plan, this would be September 3, 2019, at the latest. If the Department does not approve the program, the applicant must submit a revised proposal within 30 days. If the Department rejects the subsequent proposal, the manufacturer or drug take-back organization will be in violation of the Act and subject to enforcement, which could involve a potential fine of up to $2,000 per day of noncompliance. Overall, given the various deadlines, this process can stretch into October 2019.

From the Morgan Lewis blog, ***As Prescribed***.

Trendy Genes – Citing Surge in Cell and Gene Therapy IND Submissions, FDA Previews New Related Policies

Human cell and gene therapy research has advanced dramatically in recent years and opened the door to potential

treatments for diseases once considered incurable. On January 15, FDA Commissioner Gottlieb and Peter Marks, M.D., Ph.D., director of the Center for Biologics Evaluation and Research (CBER), issued a joint statement announcing plans to keep pace with the rapidly growing and evolving field through new policy guidance and other assistance. According to the statement, FDA is turning its attention and additional resources toward these therapies in 2019 due to a "large upswing" in the number of cell and gene therapy investigational new drug (IND) applications. Based on an assessment of the more than 800 cell-based and gene therapy INDs currently on file with the agency, FDA projects that it will receive more than 200 cell and gene therapy INDs per year by 2020, and will approve 10 to 20 such products per year by 2025.

To accommodate the uptick and to ensure regulation of firms that may be operating outside of regulatory compliance, the statement sets forth FDA's planned actions to support cell and gene therapy product development in 2019:

- **Expanded review group**. According to the statement, the agency is currently working to expand its review group dedicated to evaluating cell and gene therapy INDs, with a goal of adding about 50 additional clinical reviewers this year.
- **Expedited programs**. FDA plans to work with sponsors to utilize expedited programs, such as the regenerative medicine advanced therapy (RMAT) designation and accelerated approval. Products that receive an RMAT designation may be entitled to rolling and priority review, as well as the opportunity to have frequent meetings with FDA to discuss issues such as study design. Accelerated approval allows for earlier approval of investigational products that treat serious conditions and fill an unmet medical need based on a surrogate endpoint. While the accelerated approval pathway may offer a faster route to approval, it also permits FDA to require postmarket follow-up studies on the treatments.
- **Clinical guidance documents**. Following its issuance of six draft guidance documents in July 2018 on gene therapies, the statement proposes additional clinical guidance documents related to different areas of active product development. The plan calls for guidance on products for specific disorders and products, such as inherited blood disorders (FDA previously issued a draft guidance for hemophilia drug development in the July 2018 set), neurodegenerative diseases, and cell-based regenerative medicine products.

From the Morgan Lewis blog, ***As Prescribed***.

What Does FDA Not Have in Common with the Common Rule?

After several delays, the revised US Federal Policy for the Protection of Human Subjects (also known as the Common Rule) went into effect on January 21. The Common Rule is generally applicable to research conducted or supported by one of the federal departments or agencies that has integrated the rule into its own regulations (e.g., US Department of Health and Human Services (including the National Institutes of Health), US Department of Agriculture, US Department of Defense). Some clinical trial sites may also apply the Common Rule across all clinical research projects, regardless of funding source, through a US Office for Human Research Protections Federal Wide Assurance. Despite the mandate under the 21st Century Cures Act to harmonize FDA regulations with the Common Rule to the extent practicable and allowable under existing legislative provisions, FDA has yet to propose aligning regulations. Rather, FDA issued guidance titled Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations. As of right now, while FDA is aware of new inconsistencies between its human subject regulations and the revised Common Rule, the agency has advised that when a given study is subject to both sets of regulations, the rule that offers greater human subject protection should be applied. The guidance sets forth FDA's position on the following areas of potential discrepancies between the Common Rule and FDA regulations:

- **Informed consent**. While the revised Common Rule has changed the content and format requirements for the informed consent document, FDA states that the changes are not inconsistent with FDA's current informed consent policies and guidances, and thus two separate informed consent forms are not necessary to comply with the Common Rule and FDA regulations. Notably, FDA already proposed a rule and issued guidance generally consistent with the Common Rule regulations that permit institutional review boards (IRBs) to waive or modify informed consent documents for certain clinical investigations presenting minimal risk.
- **Expedited review**. The revised Common Rule modifies the conditions for expedited IRB review (i.e., IRB review carried out by the IRB chairperson or designee only). Under the revised Common Rule, if the investigation involves research categories deemed eligible for expedited review in the HHS/FDA 1998 list, an IRB may use expedited procedures unless the reviewer determines that the study involves more than minimal risk (i.e., there is a presumption that the research is minimal risk). Under FDA's rules, however, expedited review may only be used if the reviewer finds that the research involves no more than minimal risk (i.e., there must be an IRB minimal risk determination). As a result of this difference, IRB reviewers must continue to apply this higher standard (and associated documentation requirements) when determining the applicability of expedited review for FDA-regulated studies.
- **Continuing review**. Under the revised Common Rule, continuing review (i.e., review of research at intervals appropriate to a study's degree of risk, and at least annually) is no longer required in certain circumstances,

such as when research is eligible for expedited review. FDA, however, will continue to require IRB continuing review.

From the Morgan Lewis blog, ***As Prescribed***.

Expanded Access: FDA Steps Up to Stay In

FDA recently signaled that it plans to be more involved in facilitating expanded access to investigational new drugs. This follows the agency's announcement of its efforts to improve and clarify the expanded access program (EAP), as well as state and federal legislation intended to simplify the process to use investigational drugs for treatment purposes.

In an unconventional step, Commissioner Gottlieb announced this move in a December 14, 2018, BioCentury article, which he subsequently tweeted, stating that FDA's "goal is to facilitate and streamline the patient experience with our expanded access program; to create concierge-like service for providers and patients who are trying to get access to drugs." Part of this "concierge-like service" is a proposed program in which agency staff will field patient and physician EAP calls and complete single-patient EAP request paperwork. According to BioCentury, FDA will then send the forms to the physician for signature, forward the expanded access request to the product manufacturer, and ensure that the request is sent to an IRB (though how this will be done is not clear).

Perhaps most interestingly, based on the article, under the proposed plan, there will be an expectation that manufacturers respond to EAP requests within a yet to be determined timeframe. And, while companies will still have the discretion to provide or not provide the investigational product for EAP use, Richard Pazdur, the director of FDA's Oncology Center of Excellence, which is where the program will be piloted, was quoted saying that companies will "have to give the reason for denying access." Commissioner Gottlieb was further quoted saying that companies have an "obligation to consider expanded access, especially in areas of unmet medical need" and "[t]here are advantages for patients for FDA contacting the sponsor . . . . We can have a different conversation [with a drug company] than an individual patient or physician."

From the Morgan Lewis blog, ***As Prescribed***.

FDA Sings the Orange Book Blues to Announce a Potential New Patent Listing Approach

FDA on January 30 signaled what could be an about-face with regard to its role administering the List of Approved Drug Products with Therapeutic Equivalence Evaluation (referred to as the Orange Book). Historically, FDA's Orange Book role has been solely ministerial. However, over the next year, FDA may begin taking a more active approach to the Orange Book. FDA announced its potential new Orange Book role in a press release accompanying the publication of a draft guidance, Marketing Status Notifications Under Section 506I of the Federal Food, Drug, and Cosmetic Act (Guidance). The actual Guidance is not particularly remarkable; it largely provides instructions on the content and format of marketing status notifications under Section 506I of the Federal Food, Drug, and Cosmetic Act (FFDCA), a new addition to the statute from the FDA Reauthorization Act of 2017. As a reminder, among other provisions, Section 506I requires that drug application sponsors provide FDA with (1) 180-day prior notification before withdrawing an approved drug product from sale; and (2) notification within 180 days of a drug's approval if that drug will not be available for sale within that same timeframe. Failure to provide the required notifications can result in a product being moved from the active section to the discontinued section of the Orange Book.

More interesting, however, is how the Guidance fits into FDA's larger initiative to increase generic drug competition. Commissioner Gottlieb stated, "Having timely, accurate information about what drugs are being actively marketed helps provide transparency around circumstances where generic competition is lacking. It helps us also better understand circumstances where generic medicines are being approved, but not marketed so that we can better consider any policy reasons why this may be occurring." Thus, it appears that with the new information provided by Section 506I, FDA will be evaluating the current generic competition landscape.

For more information on the Guidance and additional FDA Orange Book proposed changes, see the blog post on ***As Prescribed***.

Falsified Medicines

On February 9 the Falsified Medicines Directive (2011/62/EU) and implementing measures— **legislation countering falsified medicines**—came into force in the European Union, under which pharmaceutical companies will be required to apply a 2-D bar code and affix antitampering devices on all prescription medicinal products. It also introduces enhanced requirements for manufacturing, such as good manufacturing practices for active substances, and stricter distribution and website controls.

IFPMA Code

The International Federation of Pharmaceutical Manufacturers and Associations' Code of Practice (Code) **has been amended effective January 1**. Now all gifts and promotional aids associated with prescription medicines for the personal benefit of healthcare professionals are banned, reversing the partial exemption for customary gifts for significant national, cultural, or religious events in order to avoid "any perception of potential influence." However, informational and educational items may be provided to healthcare professionals for their own education or for the education of patients, provided that the items do not have independent value and are not branded. The Code still

permits promotional aids of minimal value associated with OTC products, but only if it is relevant to the healthcare professional's practice. The prescription medicine restrictions have applied for some five years in the European Union (and United States) and these changes bring the code in line with other territories' practices.

The other change is the introduction of a shift from a rules-based approach to a code based on values and patients' trust, requiring the promotion of a culture of ethics and integrity between IFPMA members and the healthcare community, no matter how testing the circumstances.

EU Legislative Update: Upgraded Provisions, Antimicrobials, Temporary Measures, and Financial Penalties

New legislation, Regulation (EU) 2019/5, amends the human medicines code Directive 2001/83 and Regulation 726/2004 on the centralized procedure by moving certain provisions such as conditional marketing authorizations, variations, transfers of marketing authorizations, and financial penalties, which were previously contained in Commission regulations, into the regulation itself. It also expands the scope of Commission Regulation 658/2007 on Financial Penalties. The "upgrade" of these provisions into the legislation itself will have the effect of making those rules more difficult to modify.

Regulation 726/2004 now also contains a legal definition of "antimicrobial" and the EMA has been tasked with a more active role in reporting on use of antimicrobials and antimicrobial resistance in the European Union.

In the event an EU manufacturer fails to observe its regulatory obligations or an authority has pharmacovigilance concerns in relation to a product, the Commission should seek an EMA opinion and adopt the final decision within six months. Regulation 2019/5 also allows the Commission to take temporary measures at any time and only has to consult with the EMA. It also gives the Commission the power to adopt delegated acts with regard to the definition of the situations requiring post-authorization efficacy studies, conditional marketing authorizations, variations, transfers of marketing authorizations, and financial penalties.

Finally, Regulation 2019/5 amends Regulation 726/2004 by granting the Commission the power to impose financial penalties on legal entities such as affiliates or parents of the marketing authorization holder, or another organization involved in or that could have addressed the noncompliance.

See the **legislation**.

Changing Ownership of a Marketing Authorizations

The Medicines and Healthcare products Regulatory Agency (MHRA) has issued **updated guidance** on transferring ownership of marketing authorizations.

Medicines with an Integral Medical Device

New Q&A guidance documents on the new medical devices regulation (MDR) and in-vitro diagnostics regulation (IVDR) have been published by the EMA. The regulations will remain in the transition period until 2020 and 2022 to allow manufacturers, notified bodies, and authorities to comply with the changes. The Q&A document focuses on the implementation of Article 117 of the medical devices regulation, which stipulates that marketing authorization applications for medicines with an integral medical device must include the results of the device's assessment of conformity by a notified body.

EU-US Regulatory Convergence

An executive working group established to take forward plans to strengthen EU-US trade, which were agreed during talks between US President Donald Trump and European Commission President Jean-Claude Juncker last summer, includes commitments to close the regulatory divergences. An **interim report** states that the European Union will "take steps to make use of single audit reports . . . in a manner that is compatible with EU legislative requirements." The work of the group includes exploration of trade facilitating actions in a number of sectors, such as pharmaceuticals and medical devices, and closer cooperation on standards.

Interface Between Clinical Trials Regulation and EU General Data Protection Regulation

The European Data Protection Board (EDPB) considered the interrelationship between the EU General Data Protection Regulation (GDPR) and Clinical Trials Regulation (CTR) in an **opinion on the processing of personal data** as the primary use in the context of clinical trials, and the secondary use of such data.

The opinion states that for processing related to reliability and safety purposes, the relevant legal ground under Article 6 of the GDPR is compliance with a legal obligation.

However, the Article 6 ground is considered inapplicable to operations purely related to clinical research activities. For such activities, the EDPB suggests one of the three following legal grounds:

- **Consent**. To rely on consent under the GDPR, consent must be freely given, there should be no clear imbalance between the subject and the sponsor, and where a study subject withdraws their consent, all research activities carried out with the clinical trial data on the basis of consent should cease. Accordingly, consent under the GDPR may not be an appropriate legal ground in most cases.
- **Public interest**. The alternative legal ground of performance of a task carried out in the public interests is likely to be limited to public authorities and universities, rendering this ground unlikely to apply to a commercial company.

- **Legitimate interests**. The EDPB states that an alternative legal ground would be the legitimate interests of a sponsor. Depending on the specific circumstances, the most relevant ground under Article 9 of the GDPR (on special categories of personal data) to permit processing of health data would be either where the processing is necessary for reasons of substantial public interest in the area of public health, or where the processing is necessary for scientific research purposes.

In addition, the EDPB considered secondary uses of clinical trial data. It concluded that where personal data is further processed for scientific research purposes, even if outside the clinical trial protocol, then such use may be considered compatible if appropriate technical and organizational measures are in place so that further processing will be permitted on this basis.

It will be interesting to see how ethics committees react to the opinion, especially on the view that patient consent in most cases may not be the best legal ground for clinical trials.

Supplementary Protection Certificate Proposed Changes

The European Commission has **proposed to amend** Regulation 469/2009 on Supplementary Protection Certificates (SPCs) by the introduction of a manufacturing waiver under which EU-based companies could manufacture generic or biosimilar pharmaceutical drugs for the purpose of exporting to non-EU markets without SPC protection during the term of that SPC.

Under current rules, a medicine protected by an SPC has intellectual property rights that extend patent protection beyond the normal 20-year term of the patent, up to an additional five years. The regulation will remove the competitive disadvantages faced by EU-based manufacturers of generics and biosimilars vis-à-vis manufacturers established outside the European Union in global markets. They will be entitled to manufacture a generic or biosimilar version of an SPC-protected medicine during the term of the SPC, either for the purpose of exporting to a non-EU market where protection has expired or never existed or (during the six months before the SPC expires) for the purpose of creating a stock that will be put on the EU market after the SPC has expired.

The controversial proposal has reached the stage whereby the EU Council has approved a mandate for negotiations with the EU Parliament, and the proposal will next be submitted to the European Parliament for formal adoption. At this stage, the new rules are expected to affect only SPCs applied for on or after the date that the rules come into effect.

COMPETITION

Servier Pay-for-Delay Case

The European Union General Court recently considered several important points in a **case concerning a patent settlement and license agreement** between Servier and Krka in relation to the cardiovascular medicine Perindopril. The European Commission treated the combination of these agreements as a form of market sharing arrangement.

The court confirmed that a patent settlement agreement can be a restriction by object (i.e., without the Commission having to prove actual anticompetitive effects) where it contains (1) an inducement in the form of a benefit for the generic company, and (2) a corresponding limitation of the generic company's efforts to compete with the originator company.

However, the General Court rejected certain rulings of the Commission on three grounds:

- It is inappropriate for the Commission to define the economic market for dominance purposes as comprising only the relevant molecule, rather than by therapeutic substitutability. Over recent years, the Commission has sought to move to a molecule-based assessment, particularly in genericized markets.
- Where there is a genuine dispute involving litigation and a license agreement directly linked with the settlement of that dispute, then the Commission must prove that it is a reverse payment and show that the license fee exceeds the "normal" value of the asset traded.
- A licensing arrangement for some, but not all, EU member states in respect of which the dispute is settled does not of itself constitute a value transfer or some form of market sharing. The Commission must show that the agreement is not at arm's length as an incentive to recognize the patent in other (nonlicensed) territories.

Publication of Report on Competition Enforcement in the Pharmaceutical Sector

At the end of January 2019 the European Commission published its **report on competition enforcement in the pharmaceutical sector**.

In 2016, the European Council requested an update on the enforcement activities of competition authorities since the 2008–2009 pharmaceutical sector enquiry. Concerns included tactics to delay generic competition, pay-for-delay arrangements, price fixing, and excessive pricing.

The report notes some 29 EU and national antitrust decisions against pharmaceutical companies taken since 2009, and competition issues identified in 19 out of 80 EU mergers examined requiring identified concerns to be addressed and divestments offered. The cases include major decisions in

pay-for-delay deals and attempts to intervene against high prices for off-patent medicines such as in *Aspen* and *Flynn*. The report notes also the French actions over marketing practices as disseminating incomplete and misleading information.

Merger control interventions were made by the Commission in a number of EU mergers that could have led to price increases, in some cases requiring the companies to sell parts of their businesses to maintain price competition.

These cases are part of an ongoing testing by the European courts of various Commission approaches following the European Commission's pharma sector enquiry, in particular in relation to the pay-for-delay cases where the Commission concludes that EU competition law can intervene in patent settlement cases in certain circumstances (both under the rules on abuse of dominance and restrictive agreements).

Vertical Block Exemption Consultation

The European Commission is **consulting on the Vertical Agreements Block Exemption**. A vertical agreement is one entered into between two or more parties, each of which operates at a different level of the production chain, where the primary purpose of the agreement is to purchase and sell goods or services. Commission Regulation (EU) No. 330/2010 of April 20, 2010 sets out the conditions under which certain agreements or specific contractual clauses can be exempted from the application of Article 101(1), Treaty for the Functioning of the European Union (TFEU) (on restrictive agreements), since they are deemed to "contribute to improving the production or distribution of goods or services or to promoting technical or economic progress, while allowing consumers a fair share of the resulting benefits," in accordance with Article 101(3) of the TFEU. The aim of the consultation is to assess whether it is "still effective, efficient, relevant, [and] in line with other EU legislation and adds value." The consultation closes on May 27, 2019.

CHINA

China Reaffirms Commitment to Data Privacy for Genetic Information

by Dora Wang

In the wake of several high-profile incidents regarding data privacy and the misuse of genetic and personal information, including the case of a Chinese scientist who attracted worldwide criticism after reportedly creating the world's first human babies whose DNA is genetically modified, the Chinese government has recently issued several top-level policy directives reaffirming its commitment to strengthening cybersecurity and the protection of personal data and human genetic information and material. Though driven by recent events, these policy directives are intended to build upon and further strengthen already existing protections enshrined in the country's constitution and Tort Liability Law, a process that had already begun with the passage of the country's Cybersecurity Law (CSL) and General Principles of Civil Law in recent years. Specifically, the recent policy directives place strict prohibitions on the unauthorized use of human genetic material for research purposes and create administrative penalties for the unlawful cross-border transfer of genetic information, while simultaneously streamlining the regulatory approval process for such transfers in an effort to mitigate the impact of increased regulation on international cooperation within the life sciences industry.

Read the full **LawFlash**.

EVENTS

Reception during the BIO International Conference

June 3, 2019
Barnes Foundation, Philadelphia
For more information, contact **Steven Perdziola**.

ML Women – Life as a Woman Entrepreneur: Building Boards, Building Teams

June 4, 2019
Morgan Lewis, Philadelphia
For more information, contact **Steven Perdziola**.

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