Morgan Lewis

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Welcome to the latest issue of our *International Life Sciences Review,* produced by our life sciences lawyers in the US, Europe and Asia and covering some of the most critical developments in the pharmaceutical and medical technology sectors in the last month. If you have questions on any of these topics, please contact Paul Ranson.

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EU ORPHAN MEDICINES

The European Commission has published the Draft Regulation amending Regulation (EC) No 847/2000 as regards the definition of the concept 'similar medicinal product'.

The definition of the concept 'similar medicinal product', is relevant under Article 8 whereby a 10-year orphan exclusivity prevents health regulators from accepting an application for authorization, or granting an authorization, “for the same therapeutic indication, in respect of a similar medicinal product.”

The publication of the Draft Regulation follows last year’s public consultation on the concept of similarity. The original consultation document did not propose new definitions of the terms “similar medicinal product” and “similar active substance” but clarified the term “principal molecular structural features.” In addition, the document provided examples to define what products are considered to be similar and distinguished in this regard between chemical, biological, and radiopharmaceutical medicinal products. In addition, the document also sought to clarify the similarity in cases of ATMPs and gene therapy medicinal products. The published Draft does contain an extended definition of “similar active substance”, clarifying that “[i]f the principal molecular structural features cannot be fully established, the similarity between two active substances shall be assessed on the basis of the biological and functional characteristics”.

See the draft regulation here.

The EU Commission has also published a roadmap in December clarifying the context, purpose, scope and timelines of the evaluation of and Regulation (EC) No 141/2000 on orphan medicinal products (and Regulation (EC) No 1901/2006 on paediatrics) due for publication next year. See the roadmap here.

EU SPCS AND THE RESEARCH EXEMPTION

The European Commission also conducted a public consultation on supplementary protection certificates (SPCs) and patent research exemptions, as part of the Single Market Strategy adopted in 2015. The consultation explored a possible "recalibration of certain aspects of patent and SPC protection", which could comprise the following three elements: the creation of a European SPC right (currently they are issued nationally), an update of the scope of the EU patent research exemptions (i.e. the Bolar exemptions), and the introduction of an SPC manufacturing waiver (this waiver would allow EU-based manufacturers of generic and biosimilar medicines to compete on an equal footing with competitors from non-EU countries not covered by an SPC). See the consultation here. In December 2017, the European Centre for International Political Economy criticised the waiver proposal from the perspective of the innovative industry in that it would '*dis-incentivise originators and innovators in Europe [...] and lead to a declining commercial value of patents*'.

EU SPCS AND MEDICAL DEVICES

The European Court of Justice (ECJ) has been asked by way of a referral from a German court to decide on the availability of supplementary protection certificates (SPCs) for a combined medical device and medicinal product that has been authorised under the EU Medical Devices Directive (93/42/EEC).

The difficulty in getting SPC cover for a medical device is that under the SPC legislation the product must be "*subject... to an administrative authorisation procedure as laid down in Directive 2001/83/EC*". (2001/83 governs medicinal products rather than devices) to be eligible for SPC cover. The medicinal component in a combined medical device and medicinal product may be authorised the Medical Devices Directive but the medicinal product in the device is itself verified through a process in a manner analogous to 2001/83. National regulatory offices have taken different views as to whether this affords SPC protection to the product. The referral asks for confirmation as to whether an authorisation under 93/42 for a device containing a medicinal product can be used for an SPC where the quality, safety and efficacy of the medicinal product component has been verified in a manner analogous to the Medicinal Products Directive. A positive decision answer could therefore extend the period of exclusivity available for many medical devices with active ingredients. The case can be found (in German) here.

FRENCH COMPETITION ENQUIRY

In November 2017, the French Autorité de la concurrence (CA) announced a new enquiry into the sector broadly following its 2013 sector enquiry subjects. Topics include:

- the pharmaceutical distribution chain and the dynamic between smaller pharmacies and the growing trend of pharmaceutical companies to start Direct to Pharmacy' (DTP) selling to the large pharmacy chains;
- possibly reducing restrictions on the sale of non-prescription medicines including allowing on-line sales in the light of the perceived lack of competition in OTC products;
- the success of the scheme implemented since 2013, under which rebates have to be declared to the regulatory authorities including whether the savings made by dispensing chemists are passed onto consumers.
- the criteria used in the negotiation of reimbursable medicines;
- the bargaining power of hospitals when negotiating prices with pharmaceutical companies.

The CA normally submits non-binding public opinions up to 18 months after the launch of an inquiry. See the CA press release here.

NETHERLANDS COMPULSORY LICENCE PROPOSAL

The Netherlands Council for Public Health and Society ("RVS") has indicated that its Government might wish to enforce compulsory licences where medicine prices are not "socially acceptable" (this is not defined). The RVS' proposal is aimed new, patent-protected, medicines, including 'blockbusters' and orphan drugs (medicines for very rare diseases affecting less than five out of 10,000 people in the EU population).

The RVS point out that Article 8 of the Agreement on Trade-Related Aspects of Intellectual Property Rights for the Regulation of Intellectual Property (TRIPs Agreement) allows measures that protect public health or prevent the abuse of intellectual property rights resulting in the unreasonable restraint of trade or of international transfer of technology and at Article 31 envisages national rights to use the subject matter of a patent without the rights holder's authorisation, provided rights holders are remunerated for the licence based on the "economic value of the authorisation".

The RVS proposal is not a new concept and in the past the Commission has stated that dealing with high prices in this way is a matter to be dealt with at national level and that the Commission is not competent to deal with it. See the proposal here.

MANAGING BREXIT

- **Regulatory Briefing** - The House of Commons Library has published a briefing paper which provides an overview of current medicines regulation in the UK, the relationship with the European Medicines Agency (EMA) and other international agencies. The briefing paper can be found here.

- **EMA to Amsterdam -** The European Medicines Agency (EMA) will relocate to Amsterdam as part of arrangements being put in place ahead of the UK's withdrawal from the EU.

- **Data Transfer -** The UK Information Commissioner (ICO) has confirmed its view that Brexit will not invalidate intra-company data transfer arrangements outside the EEA, based on binding corporate rules (BCRs). BCRs are the contractual commitments between businesses and data protection authorities whereby the business commits to processing personal data in accordance with EU data protection laws. With the General Data Protection Regulation (GDPR) applying from 25 May 2018, BCRs will need to reflect the GDPR requirements. See the ICO position here.

- **Customs –** Whilst the precise nature of the UK's future customs relationship with the EU will depend on the outcome of ongoing UK and EU negotiations, the UK Government has published the draft Taxation (Cross-border Trade) Bill intended to underpin the UK's possible independent post-Brexit customs and cross border VAT and excise legislation regime. See the bill here.

- **Life Sciences Sector Deal –** In the wake of the UK Life Sciences Strategy (see Issue 7 here) the recently published new overall industrial strategy (see here) has highlighted life sciences as one of its six post-Brexit growth sectors and the first to benefit from a 'sector deal' intended to promote close collaboration between industry and the NHS, support for life sciences 'clusters', the establishment of new digital innovation hubs, closer working between the industry and the NHS, a new research initiative, the Health Advanced Research Programme (HARP) seeking solutions to the major forthcoming healthcare challenges and a new Office for Artificial Intelligence will be created and focus on six priority business sectors, one of which is life sciences. Whilst laden with good intentions, the sector deal is arguably light on detail – it may be found here.

- **Commission Guidance** - The European Medicines Agency (EMA) and the European Commission have published updated guidance (originally issued in May 2017) intended to help pharmaceutical companies prepare for Brexit so as to avoid any impact on the continuous supply of medicines for human and veterinary use within the EU and to allow for the continued marketing of those medicine in the European Economic Area (EEA) after Brexit. See the guidance here.

EU AND US MEDICAL DEVICES REGULATION

- **Regulation Roadmap** - Competent Authorities for Medical Devices ("CAMD") has published a roadmap on the implementation priorities for the Medical Devices Regulation MDR and IVDR (May 2020 and May 2022 respectively). This includes a new MDR/IVDR implementation taskforce with the aim to facilitate EU cooperation during the implementation phases. There are seven workstream including clinical evaluation, classification, Notified Bodies, Eudamed (the portal where EU competent authorities enter information received from manufacturers and notified bodies in order to exchange the information with the European Commission), vigilance and IVD-specific issues It is also highlighted by the roadmap that although the MDR and IVDR provide for the adoption of specific implementing acts, it is envisaged that additional advance guidance might be needed. The roadmap can be found here.

- **Notified Body Codes** - The MDR and IVDR required the European Commission to draw up a list of codes and corresponding types of device so as to categorise the fields of expertise of the Notified Bodies and thereby designate their scope. When Notified Bodies submit their application forms, available on the website of the Notified Body Operations Group, they are required to list the scope of their planned activities by choosing the relevant codes. The eventual designations will determine which Notified Medical will be eligible to approve device manufacturers' products.

- **Software as a Medical Device –** Last December, following a referral by the French Council of State, the Court of Justice of the European Union (CJEU) gave judgment on a question as to whether drug prescription and dispensing software qualifies as medical device within the meaning of the Medical Devices Directive (Directive 93/42).

The CJEU confirmed that software is a medical device if it both a) is intended to be used for a medical objective); and b) does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means. On the first criterion, the CJEU found that the software in dispute pursues a specifically medical objective as it cross-references patient-specific data with the drugs that the doctor is contemplating prescribing. On the second, the CJEU concluded that a device need not act directly in or on the human body and the essential test for being classified as medical device is the software's purpose.

Accordingly, the Court decided that software which makes it possible to use patient-specific data for the purposes of detecting contraindications etc, can be a medical device under Directive 93/42, even if such software does not act directly in or on the human body.

Software simply performing storage, archiving, compression or simple search are not considered devices but were where it goes beyond these functions and performs any modification or interpretation of the data, it is likely to be recognized as medical device.

See the judgment here.

- **New FDA Guidance on Using IVDs in Clinical Trials -** Companies conducting clinical trials under an Investigational New Drug application (IND) in which unapproved *in vitro* diagnostics (IVDs) are used should be aware of new FDA Guidance on Investigational IVDs Used in Clinical Investigations of Therapeutic Products. The Guidance emphasizes that pharmaceutical companies using unapproved IVDs in clinical trials must assess the risk of the IVD before initiating the trial, address it with the relevant IRB, and may need to file an Investigational Device Exemption (IDE) request with the FDA before the clinical trial will be allowed to commence. For more information, see Morgan Lewis's recently issued LawFlash.

EU ADVANCED THERAPY MEDICINAL PRODUCTS

The European Commission's Directorate-General for Health and Food Safety and the European Medicines Agency (EMA) have published a joint action plan to foster the development of advanced therapy medicinal products (ATMPs) governed by Regulation 1394/2007 on advanced therapy medicinal products.

The main aim is to streamline procedures and better address the specific requirements of ATMP developers. It was accepted that whilst the Regulation had protected patients from unsound treatments there were still shortcomings impeding the translation of scientific progress into medicinal products available to patients.

The plan contains 19 actions in different key areas. Some of the actions are already in place such as dialogue on clinical trials and health technology assessment, others are new including the initiation of dialogue with national competent authorities to address the potential discrepancies between the legislation on genetically modified organisms (GMO) and on medicines and the introduction of an EU Commission guideline on good manufacturing practice for ATMPs.

See the plan here.

CHANGES IN US/EU INSPECTION PRACTICE

FDA Recognition of EU Inspections - From November 1, 2017, the U.S. Food and Drug Administration (FDA) has recognized inspections conducted by European Union drug regulatory authorities. Specifically, FDA is recognizing manufacturing facility inspections conducted by drug regulatory authorities in Austria, Croatia, France, Italy, Malta, Spain, Sweden, and the United Kingdom. This step is part of the renegotiation of the Pharmaceutical Annex to the 1998 Mutual Recognition Agreement, which was finalized in the spring of 2017.

While important to ensure the quality of the drug supply chain, regulatory authority inspections can be burdensome and disruptive for manufacturers. Inspections can divert company time and attention from daily operations and quality responsibilities. While the exact impact of the FDA's partnering with EU drug regulatory authorities is yet to be seen, these efforts should introduce efficiencies into the inspection process, for both the regulators and regulated industry. See the FDA announcement here.

FDA International Inspections - Some valuable insights relating to FDA ex-US inspections have come from the November 2017 12th Annual FDA Inspection Summit, as reported by the December 2017 Drug GMP Report.

The FDA Assistant Commissioner, Ellen Morrison stated that the FDA Program Alignment initiative may well result in FDA's future inspectional efforts being focused outside the United States with FDA inspectors being more specialized and more likely to work outside of the United States.

Under the Program Alignment initiative, the FDA's Office of Regulatory Affairs is using a program-based management structure, in which staff are organized by regulated product category. According to the FDA, this specialization is necessary given growing complexity of FDA regulated products, the numerous product markets, and the more intricate rules governing FDA's actions.

Companies can expect inspectors to have greater expertise in the category of products under inspection. While this additional expertise may eliminate inspectional observations that are due to technical misunderstandings, companies may find that inspectional observations become more nuanced, detailed, and specific. Documentation requests may be more precise and focused. Accordingly, as always, Companies should ensure that their quality systems and processes are up to date, that all personnel are adequately trained, and that the necessary records and documentation are maintained so that facilities remain in an inspection ready state. Assistant Commissioner Morrison's presentation can be viewed here and the questions and answers on the Office of Regulatory Affairs Program Alignment initiative here

In addition, Douglas Stearn, the Director FDA Office of Enforcement and Import confirmed that manufacturing data integrity continues to be a top priority for the Agency.

Specific integrity issues cited included the use of “unofficial” systems (e.g., the use of outside batch blending to bring batches within specifications, and raw data and results that are created outside of a company’s quality reporting system); documentation that is questionable, false, or includes omissions; missing deviation data; and the lack of safeguards to protect data.

Whilst acknowledging that cross border prosecution can be a challenge for FDA due to limits on subpoena powers, evidentiary issues, and jurisdictional issues, the Agency can still take enforcement actions against foreign manufacturers who introduce drug products into U.S. interstate commerce or work through regulatory authorities in the resident country.

These powers highlight the need for document accountability in the manufacturing process, adequate training of all employees and contractors, prompt investigation, remedy and recording all deviations from approved processes, policies, and procedures and periodic internal data integrity audits. Douglas Stearn’s presentation can be viewed here.

TOUGH NEW DRAFT FDA HOMEOPATHIC GUIDANCE

On December 18, 2017, the FDA published a draft document regarding the Agency's new position on the sale of homeopathic drugs in the United States. FDA notes that it had previously identified homeopathic products as a distinct category of drugs under its regulatory scheme, and deferred consideration of them. Accordingly, homeopathic products were never formally approved by FDA, and not otherwise considered generally recognized as safe or effective for use in the U.S.

The new draft guidance simply states that all homeopathic products are being marketed illegally and describes FDA's new risk-based approach to enforcement whereby FDA will focus on homeopathic products (1) with reported safety concerns, (2) that contain or purport to contain ingredients associated with potentially significant safety concerns, (3) intended to be administered other than orally and topically, (4) intended to be used for serious and/or life-threatening diseases or conditions, (5) for vulnerable populations, and (6) that are deemed to be adulterated. The draft guidance makes no distinction between those products marketed over-the-counter and those marketed by prescription under the supervision of a medical practitioner in connection with the proposed enforcement priorities, nor does it provide the clear marketing guidelines set forth in the guidance currently in effect for homeopathic drugs.

The new may be found here. The lack of clarity in FDA's new enforcement approach towards homeopathic medicine has the potential to create confusion in the marketplace. Thus, those currently marketing or considering marketing such products should consider seeking clarification through the submission of comments during the public comment period which ends on 18 March 2018 - see here.

In Europe, homeopathic remedies are subject to a simplified national traditional use registration schemes.

RELEVANCE OF FOREIGN LAWS IN US ANTI-TRUST

Potentially impacting the reach of US antitrust enforcement, the US Supreme Court will determine standards to apply in considering a foreign government's legal statement concerning the interpretation of its domestic law in price fixing and other cases.

This case stems from a series of lawsuits that were filed in 2005 against four Chinese manufacturers of vitamin C imported into the United States, alleging that the Chinese companies had colluded on export prices and volumes. The defendants argued that Chinese laws and regulations required them to coordinate regarding their export prices and volumes and awarded $147 million damages against the companies. The Chinese Ministry of Commerce submitted to the District Court interpretation of Chinese law that supported the defendants' position but the Court concluded that Chinese law did not require the companies to collude.

The US Supreme Court agreed on January 12 to review the District Court decision to consider the degree of deference owed to foreign governments' interpretations of their own laws in US legal proceedings. This outcome may herald potential changes in the manner in which foreign laws will be interpreted in international antitrust cases.

See a fuller report here.

CHINA – UNFAIR COMPETITION AND BRIBERY

The pharmaceutical industry is well aware of the challenges of bribery allegations in China and the Chinese government has recently introduced its first substantial amendments to its Anti-Unfair Competition Law (AUCL) dating from 1993.

In particular:

- "Unfair competition" has been defined to include not only the impact on competitors but also infringement of legitimate consumer rights and interests;
- The context in which "Bribes" can be made and their purpose has been extended from "selling or purchasing products" (i.e. transaction-related) to a broader "seeking business opportunities or competitive advantage";
- "Bribe Receivers" now specifically include third party intermediaries with the authority or influence to enable the giving and receiving of improper payments;
- Whilst individuals should be held accountable for carrying out the act of bribery, the corporate entity they work for has a responsibility of monitoring and supervising their employees to prevent corruption and/or bribery and has a burden of proof of demonstrate appropriate compliance controls over employees. This reflects FCPA and UK Bribery Act corporate requirements;
- Commissions and discounts in a transaction must be accurately recorded by both parties although any failure to record would be considered to be an offence under accounting rules rather than bribery *per se* under the AUCL;
- There are enhanced enforcement powers including entry into premises, seizing assets, access to bank details, fines for obstruction of an investigation and higher penalties for breach including fines, business licence suspension and black listing.

A fuller Morgan Lewis report on these AUCL changes can be found here.