Q&A Follow-up from Cross-Border Life Sciences Collaborations in China

Presented by Lester Ross, Kenneth Zhou and Belinda Juran

Partners Lester Ross and Kenneth Zhou of WilmerHale's Beijing office, along with Boston Partner Belinda Juran, discussed the licensing and legal environment in China for life sciences companies in two webinar sessions on May 8 and May 30, 2018. Our speakers answered questions received during the webinar below.

Has the (former) CFDA provided guidelines for development of cellular therapies? Will these now follow an IND-type process? How will they regulate cell therapies?

WH: Yes. The former CFDA promulgated the *Principles of Technical Guidelines on Research and Evaluation of Cellular Therapies Products* (总局关于发布细胞治疗产品研究与评价技术指导原则的通告http://samr.cfda.gov.cn/WS01/CL0087/220082.html) on December 18, 2017, followed by the *Key Points with respect to Pharmaceutical Research in Clinical Trials and Submission of Application Documentation* (CFDA Center of Drug Evaluation, March 2018, 细胞治疗产品申请临床试验药学研究和申报资料的考虑要点, http://www.cde.org.cn/news.do?method=largeInfo&id=314382). These two documents provide the framework with respect to the development of cellular therapies including the clinical trial application procedure. In particular, they provide detailed guidance on the approval of applications in a number of areas, including pharmaceutical research, pre-clinical research, and clinical research, production materials standards, product quality release test standards, and selection of animal models for non-clinical studies and risk management. Cell therapy products as described in the Guidelines refer to living cell products that are used for the treatment of human diseases, the source and clinical operation of which are in accordance with ethical requirements; and the development and registration of which are in accordance with drug administration regulations. The Guidelines do not apply to blood components used for blood transfusion, unprocessed hematopoietic stem cell transplantation, reproductive cells, and tissues and organ products composed from cells. These documents set standards for the approval of clinical trials for cell

therapies and open the door to commercialization of cell therapies subject to SDA regulation, much like other new drugs. http://www.pharmexec.com/china-s-car-t-therapy-race

Does the change mean that foreign drug companies can now conduct Phase I clinical trials in China before they have done so outside China first?

WH: No. Although foreign applicants for new chemical drugs and new therapeutic biological products may now conduct a full clinical development plan in China (starting from first-in-human to proof-of-concept (PoC) trials) under the *Decisions for Adjusting the Administration Regime for Imported Drug Registration* (former CFDA, October 2017), foreign drug companies may only conduct Phase I trials in China in parallel with the global development program, not before they have done so outside China. This change effectively opens the Phase I market in China. However, vaccines are still barred from conducting global trials in China.

If a US company sets up a joint venture (JV) or subsidiary in China, which goes public there, how difficult would it be to get some of the proceeds or capital out and back to the US parent?

WH: It will take some time for the audit to be completed, the board to approve the distribution, payment of withholding tax and obtaining proof thereof, and then getting bank clearance. If the amount is very large, local foreign exchange quotas may further slow foreign exchange remittances. Nevertheless, the foreign shareholder of a foreign-invested company is entitled to remittance of its share of the proceeds and declared dividends received from its JV or China subsidiary after the 10% withholding tax is paid. We would, however, generally recommend investing through a four-tier structure in which the US parent (Tier1) establishes an offshore holding company in a tax-favored common law jurisdiction like the Caymans or BVI (Tier 2), then below that have the top-tier holding company establishes a wholly-owned second-tier holding company in Hong Kong, Singapore or other jurisdiction which may be eligible for Chinese tax preferences (Tier 3), and then below that establish a wholly foreign-owned enterprise in China to conduct the business (Tier 4). This reduces the need for Chinese government approvals of changes in company structure and shareholdings while facilitating an offshore public listing if the company decides that an offshore listing is preferable.

Could you describe how to perform diligence on Chinese Counterparties?

WH: We recommend engaging an investigation company through your law firm to conduct a non-intrusive, non-pretextual investigation of Chinese counterparties while also engaging your law firm to review publicly available document on the counterparties' corporate structure, shareholdings, and finances. Several companies provide such service.

On what data was Gardasil approved, based on conditional approval? Chinese patients only, global package or both?

WH: The conditional approval on Gardasil 9 was granted based on (1) Gardasil data that previously led to the quadrivalent HPV vaccine approved by SDA in May 2017, which samples for both Chinese patients and foreign patients; and (2) foreign clinical trial data specific to Gardasil 9 which is supposed to be targeted to foreign patients under Hainan Province's pilot medical tourism zone, although it is unclear whether treatment even at this stage will be restricted to foreign patients. The conditional approval comes with requirements for additional studies and post-marketing surveillance.

Please provide a reference to the cellular therapy guidelines mentioned?

WH: Here is the link to the cellular therapy guidelines.
http://samr.cfda.gov.cn/WS01/CL0087/220082.html
(总局关于发布细胞治疗产品研究与评价技术指导原则的通告)

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