君合研究简讯

JUNHE

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医药健康领域法律热点问题

鼓励药品医疗器械创新重磅政策正式落地

国务院于 2015 年发布的《国务院关于改革药品医疗器械审评审批制度的意见》（国发[2015]44号）正式拉开了中国药品医疗器械审评审批改革的大幕。在国家食品药品监督管理总局（下称“**总局**”）于 2017 年 5 月 11 日和 5 月 12 日两日内发布的四个关于鼓励药品医疗器械创新相关政策的征求意见稿（下称**“《征求意见稿》”**）的基础上，中共中央办公厅、国务院办公厅于 2017 年 10 月 8 日发布《关于深化审评审批制度改革鼓励药品医疗器械创新的意见》（下称**“《意见》”**）。以促进药品医疗器械产业结构调整和技术创新，提高产业竞争力，满足公众临床需要为目的的制度改革将进一步深化。

《意见》全文共三十六条，针对当前药品医疗器械创新面临的突出问题，着眼长远制度建设，是一份重要纲领性文件。《意见》主要包括六大方面的改革内容：改革临床试验管理；加快药品医疗器械上市审评审批；促进药品创新和仿制药发展；加强药品医疗器械全生命周期管理；提升技术支撑能力；加强组织实施。

一、改革临床试验管理

1、 临床试验机构资格认定改为备案制

《意见》明确规定，临床试验机构资格认定改为备案制，无需再由总局审批，体现了政府监管理念从事前的监管向事中、事后全过程监管的思路转变，以此提高效率，增加临床试验机构数量。另外《意见》明确放开非医疗机构成为临床试验机构的限制，鼓励社会资本设立临床试验机构，支持医学研究机构、医药高等学校开展临床试验，允许境外企业和科研机构在我国依法同步开展新药临床试验。

《意见》要求注册申请人提出临床试验申请前，应先将临床试验方案提交临床试验机构伦理委员会审查批准。

2、 改革临床试验的审批由明示许可改为默示许可

《意见》要求审评机构在受理药物临床试验和需审批的医疗器械临床试验申请前，应与注册申请人进行会议沟通，提出意见建议。在受理临床试验申请后一定期限内，食品药品监管部门未给出否定或质疑意见即视为同意，注册申请人可按照提交的方案开展临床试验。但是该“一定期限”的具体时间跨度尚待后续实施性法规进一步明确。

二、加快上市审评审批

1、 临床急需、罕见病治疗药品医疗器械的加快上市

现有的《总局关于解决药品注册申请积压实行优先审评审批的意见》、《医疗器械优先审批程序》规定，临床急需、罕见病治疗药品医疗器械可以进入相关优先审批程序。《意见》进一步提出，对于临床急需药品医疗器械，临床试验早期、中期指标显示疗效并可预测其临床价值的，可附带条件批准上市；对于罕见病治疗药品医疗器械，可提出减免

临床试验的申请。对境外已批准上市的罕见病治疗药品医疗器械，可附带条件批准上市。

2、 不再单独审批原料药、药用辅料、药品包装材料

根据 2017 年 9 月 29 日发布的《国务院关于取消一批行政许可事项的决定（国发〔2017〕46 号）》，药用辅料、直接接触药品的包装材料和容器注册审批已被取消。《意见》进一步明确原料药、药用辅料和包装材料在审批药品注册申请时一并关联审评审批，不再发放原料药批准文号。

三、促进药品创新和仿制药发展

1、 药品专利链接制度、药品专利期限补偿制度试点与药品试验数据保护制度

《意见》要求药品注册申请人提交注册申请时，应在规定期限内告知相关药品专利权人。若专利权存在纠纷，当事人可以向法院起诉，期间不停止药品技术审批。食品药品监管部门根据法院生效判决、裁定或调解书作出是否批准上市的决定；超过一定期限未取得生效判决、裁定或调解书的，食品药品监管部门可批准上市。《征求意见稿》中原规定药品注册申请人在提出注册申请后 20 天内告知相关药品专利权人，药品审评机构收到司法机关专利侵权立案相关证明文件后，可设置最长不超过 24 个月的批准等待期。《意见》将《征求意见稿》中相关期限删去，程序上更为模糊，需待药品专利链接制度的实施性规定进一步明确。

另外《意见》明确选择部分新药开展试点，对因临床试验和审评审批延误上市的时间，给予适当专利期限补偿。这一规定是为了补偿从研发开始到最后上市过程中审批时间对专利保护时间的占用。

药品试验数据保护制度是指对创新药、罕见病治疗药品、儿童专用药、创新治疗用生物制品以及挑战专利成功药品注册申请人提交的自行取得且未披露的试验数据和其他数据，自药品批准上市之日起计算给予一定的数据保护期。数据保护期内，不批准其他申请人同品种上市申请，申请人自行取得的数据或获得上市许可的申请人同意的除外。

药品试验数据保护制度与药品专利链接制度、药品专利期限补偿制度均是对药品创新权益的保护，三者组合实施，以鼓励药品创新研发。

2、 公布药品相关信息

《意见》明确将（1）建立上市药品目录集，载明新批准上市或通过仿制药质量和疗效一致性评价的药品的相关信息；（2）定期发布专利权到期、终止、无效且尚无仿制申请的药品清单。药品相关信息的公布将对促进仿制药发展产生指导作用，特别是后者的发布可以引导仿制药研发生产。

四、加强药品医疗器械全生命周期管理

1、 上市许可持有人制度全面实施

2015 年 11 月 4 日，第十二届全国人民代表大会常务委员会第十七次会议授权国务院在北京、天津、河北、上海、江苏、浙江、福建、山东、广东、四川十个省、直辖市开展药品上市许可持有人制度试点。2016 年 6 月 6 日，国务院办公厅发布了《药品上市许可持有人制度试点方案》，规定上述试点区域内的药品研发机构或者科研人员可以申请取得药品上市许可及药品批准文号，成为药品上市许可持有人，试点工作实施至 2018 年 11 月 4 日。在上市许可持有人制度推行后，药品注册与生产许可不再捆绑，持有人和生产企业可以是不同的企业。持有人拥有上市许可药品的财产权，有权自行或指定生产商、经销商生产和经销许可药品，同时对药品全生命周期的安全性和有效性担责。

《意见》要求及时总结药品上市许可持有人制度试点经验，推动修订《药品管理法》，力争早日在全国层面实施药品上市许可持有人制度。《意见》还提出允许医疗器械研发机构和科研人员申请医疗器械上市许可。

2、 上市许可持有人在全生命周期管理中的责任承担

《意见》强调要落实上市许可持有人法律责任。药品上市许可持有人须对药品临床前研究、临

床试验、生产制造、销售配送、不良反应报告等承担全部法律责任；医疗器械上市许可持有人须对医疗器械设计开发、临床试验、生产制造、销售配送、不良事件报告等承担全部法律责任。受药品医疗器械上市许可持有人委托进行研发、临床试验、生产制造、销售配送的企业、机构和个人，须承担法律法规规定的责任和协议约定的责任。

3、 强调规范学术推广行为

《意见》中首次明确有关医药代表的两个备案：即（1）药品上市许可持有人须将医药代表名单在食品药品监管部门指定的网站备案；以及（2）医药代表的学术推广活动应在医疗机构指定部门备案。

为规范学术推广行为，《意见》再次强调禁止医药代表承担药品销售任务，以医药代表名义进行药品经营活动的，按非法经营药品查处；同时《意见》还禁止向医药代表或相关企业人员提供医生个人开具的药品处方数量；禁止医药代表误导医生使用药品或隐匿药品不良反应。

五、提升技术支撑能力

1、 审查人员的保密义务

《意见》指出，参与药品医疗器械受理审查、审评审批、检查检验等监管工作的人员，对注册申请人提交的技术秘密和试验数据负有保密义务。违反保密义务的监管工作人员将承担相应法律责任，甚至可能被追究刑事责任。监管机构应完善对注册申请材料的管理，确保审阅、复制情况可追溯。

2、 检查部门分工

《意见》对监督和检查药品医疗器械各个过程及规范执行情况进行了分工。药品医疗器械研发过程、药物非临床研究质量管理规范（GLP）、药物临床试验质量管理规范（GCP）和医疗器械临床试验质量管理规范执行情况，由国家食品药品监管部门组织检查。药品医疗器械生产过程和药品、医疗器械生产质量管理规范（GMP）执行情况，由省级以上食品药品监管部门负责检查。药品医疗器械经营过程和药品、医疗器械经营质量管理规范（GSP）执行情况，由市县两级食品药品监管部门负责检查。

六、总结

可以预见的是，《意见》的发布必然会引领更多实施性的法规和政策的发布。例如紧跟《意见》的发布，2017 年 10 月 10 日，总局发布《关于调整进口药品注册管理有关事项的决定》。其调整的事项主要有三个方面：一是允许同步研发申报，除预防用生物制品外，允许在中国境内外同步开展 I 期临床试验；二是优化注册申报程序，在中国进行的国际多中心药品临床试验完成后，申请人可以直接提出进口药品上市注册申请；三是对于提出进口临床申请、进口上市申请的化学药品新药以及治疗用生物制品创新药，取消应当获得境外制药厂商所在生产国家或者地区的上市许可的要求。

《意见》以及后续实施性政策的发布反应了中国政府深化改革药品医疗器械审评审批制度的力度和决心。这些措施将极大激发医药研发的活力，提供我国医药产业的创新发展水平，解决临床急需药品和医疗器械短缺难题。

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Life Sciences Industry

China Releases Reform Policies to Encourage Innovation of Pharma and Medical Devices

The China government continues its efforts to further reform of the review and approval system for pharmaceuticals and medical devices, as well as to encourage innovation in these industries. On October 8, 2017, the State Council released *Opinions Concerning Furthering the Reform of the Review and Approval System and Encouraging Innovation in Pharmaceuticals and Medical Devices* (the "Policies") based on drafts published earlier this year. The Policies aim to upgrade and optimize industrial infrastructures, to promote innovation in pharmaceuticals and medical devices, to enhance competitiveness of the industries of pharmaceuticals and medical technology and to meet the needs of the public for clinical uses of pharmaceuticals and medical devices. The Policies focus on (i) reforming administration of clinical studies; (ii) expediting the review and approval process for pharmaceuticals and medical devices; (iii) promoting innovation as well as production of generic products; (iv) strengthening regulatory oversight of the pharmaceutical and medical devices industries throughout the product lifecycle and (v) improving technical support for the review and approval process of pharmaceuticals and medical devices. The key measures include deregulating clinical studies, protecting intellectual property and data, and defining the responsibilities of the Marketing Authorization Holders (the "MAH").

I. Reforming administration of clinical studies

- The Drafts proposed that clinical study sites should no longer be required to be certified and approved, but rather implemented by a simple filing process. The Policies uphold this policy and also encourage hospitals and medical academic institutions to conduct clinical

studies. Foreign companies and institutions are permitted to conduct clinical studies in China as part of multi-regional clinical trials (MRCT).

- Ethics committee approvals are a condition of applying for the Clinical Trial Approval. Reviewers are required to communicate with applicants and give comments before they accept applications. Once accepted, if the reviewers fail to deny approval within the given deadline, applicants will be permitted to conduct clinical trials. However, it is not clear yet how deadlines will be set.

II. Expediting the review and approval process for pharmaceuticals and medical devices

- The Policies authorize accelerated approvals, with certain conditions, of drug and device products that are urgently needed. Orphan pharmaceuticals and devices may be exempted from clinical trials or be permitted to conduct simplified trials. Those products that have already been marketed in other countries may be approved by the CFDA with certain conditions and follow-up trials.
- Registration of active ingredients, excipients (inactive ingredients), and packaging materials for pharmaceutical products will be approved along with the relevant pharmaceuticals, but no longer separately issued.

III. Promoting innovation as well as encouraging production of generic products

- China will set up a catalogue of marketed pharmaceuticals, including newly approved pharmaceuticals and generic drugs that have passed the consistent evaluations of quality and efficacy.
- The patent linkage system will be adopted. When filing drug registration applications, the applicant must disclose all patents that may be involved and their status, and inform patent holders. However, it remains highly uncertain whether such requirements will be strictly enforced. Further, the CFDA continues its review process in case of a pending law suit brought by a patent holder against the applicant. The CFDA may even approve the generic product if the lawsuit against the applicant is not concluded by the deadline. From the perspective of innovative drug manufacturers, such policies may raise concerns about patent enforcement in China.
- Certain innovative pharmaceuticals may be selected for compensation with additional protections for the period of time required for clinical trials and regulatory reviews.
- Undisclosed clinical data for certain

products such as innovative pharmaceuticals, orphan pharmaceuticals and pediatric pharmaceuticals may be granted a protection period. During such period, no applications for the same product will be approved. The Policies are silent on how long the protection period may be.

- China will continue to encourage production of generic products in order to increase public access to pharmaceuticals.

IV. Strengthening regulatory oversight of pharmaceuticals and medical devices throughout the product lifecycle

- The MAH system for pharmaceuticals and medical devices will be implemented in all provinces. Under the MAH system, it is no longer required that a drug or device approval holder possess GMP-certified manufacturing facilities.

- The Policies made clear that the MAH will be ultimately liable for a pharmaceutical or medical device for the product's entire lifecycle -- including pre-clinical studies, clinical studies, manufacturing, distribution and adverse event reporting, and it will be responsible for the activities of third party contractors, such as CROs and CMOs.

V. Improving technical support for the review and approval process of pharmaceuticals and medical devices.

- The Policies emphasize the confidentiality obligations of reviewers. All officials involved in the review process must keep the technical information and clinical trial data strictly confidential.

- The enforcement against non-compliance with GCP, GMP and GSP will continue to be rigorous. It is clarified that the GCP compliance is supervised and enforced by the national CFDA. Provincial FDAs are responsible for enforcing GMP compliance and FDAs at the municipal level or county level responsible for enforcing GSP compliance.

In addition, the Policies address the role of medical representatives in drug promotion, which has been heavily debated in the industry. According to the Policies, medical representatives can only provide academic information about pharmaceuticals and collect feedback from clinical use. They must not have any responsibility for the sales performance of pharmaceuticals. All academic promotional activities must be conducted openly and filed with relevant departments within medical institutions.

It should be expected that more detailed regulations and rules will be released for implementation purposes. For example, on October 10, 2017 the CFDA published, a few initiatives to reform the approval process for imported pharmaceuticals (the "Circular"). The

highlights are:

(i) Previously, an MRCT in China could be approved by the CFDA only after the drug was in a Phase II or Phase III trial or had been approved in a foreign country. No such requirement will apply after the Circular, except for biological products for prevention purposes. It means that a Phase I trial may be conducted in China as part of the MRCT.

(ii) The Circular permits applicants to apply for pharmaceutical approvals once the China portions of the MRCT are completed.

(iii) For clinical trial approval and drug approval purposes, it is no longer required that the product has been approved in a foreign country if the products are innovative chemical pharmaceuticals or innovative biologicals for treatment purposes.

The Policies and follow-up regulations reflect the China government's determination and efforts to reform the regulatory system for pharmaceuticals and medical devices. With these new policies, the Chinese government expects to see more pharmaceutical and medical device companies invest and engage in R&D activities, and to further improve the safety and quality of pharmaceuticals and medical devices in the China market.

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