Ｄａｔｅ：Aug. 29, 2016

致： 中国食品药品监督管理总局， 国家卫生与计划生育委员会

To: ＣＦＤＡ， ＮＨＦＰＣ

自： 美国先进医疗技术协会（AdvaMed），医疗影像及技术联盟（MITA），

美中贸易全国委员会（USCBC），欧洲医学技术联盟

事由：关于《医疗器械临床试验质量管理规范》实施中的问题及我们的建议

Subject：issues in the implementation of “Good Clinical Trial Practice for Medical Devices” (GCP) and our suggestions

尊敬的食药监总局和国家卫计委领导：

Respected CFDA and NHFPC leaders,

今年６月１日，贵方联合颁布的《医疗器械临床试验质量管理规范》(以下简称“规范”)正式实施。该“规范”在加强对医疗器械临床试验的管理上起到积极作用，对此我们表示赞赏。然而，我们发现在最近有关部门组织的对“规范“的几次培训中，由于监管方和企业对“规范”中某些问题在解读和理解上存在一定差异，导致我们会员企业在实际操作过程中遇到了一些困惑和难以解决的问题。因此，恳请贵方对这些问题予以关注并解决。

The“Medical Device Clinical Trial Quality Management Norms” (or “Good Clinical Trial Practice for Medical Devices” (known as new China GCP) jointly issued by your sides became implemented from June 1 this year. We commend that the new China GCP has played an active role in strengthening the clinical trial for medical devices. However, we found that in a number of trainings organized by relevant departments,

due to the difference in interpreting and understanding some items in the new China GCP between the regulating agencies and the related firms, it has led to some confusions and problems hard to be resolved for our members during the actual practice. Therefore, we would appreciate your attention to and solution to these problems.

1. 新旧法规如何衔接或过渡的问题 Issue of how to connect and transit from the old to new regulations

贵方在“规范”发布的同时，也发布了《关于贯彻实施《医疗器械临床试验质量管理规范》的通知》（食药监办械管〔2016〕41 号）。 文中提到在 2016 年 6 月 1 日之前开展的医疗器械临床试验，应按照原《医疗器械临床试验规定》（简称“规定”）进行检查。但“规定”中未明确 “开展”的定义，而各临床试验管理机构通行作法是以提交临床试验机构伦理委员会审查日期为准。在最近的有关法规解读和培训中，有的监管单位提出即便在 2016 年 6 月 1 日之前开展的医疗器械临床试验，已经按照旧法规框架通过了伦理审批，甚至已经提交备案或审批的临床试验申请，也应当予以退审并按照新“规范”进行重新申报。

While the new GCP was being issued, you have also issued the “Notice on carrying out and implementing “new China GCP” （CFDA BanXieGuan〔2016〕#41）. The notice said that the clinical trials for medical device that started before June 1, 2016 should be inspected according to the old “Clinical Trial for Medical Device regulation”. However, the old regulation did not define “"carry out”. The normal practice of all clinical trial management agencies is to take the date of submitting the ethical inspection to the clinical trial institutions as the starting date. In recent regulatory interpretation and trainings, some regulating agency mentioned that applications for clinical trial should be returned for resubmission in observation of the new GCP even though these clinical trial for medical devices were carried out, approval granted by the ethic committee, or even the filing or application for clinical trials submitted before June 1, 2016 according to the old regulation.

我们认为这种说法有待商榷，因为它不符合法不溯及既往的原则。同时也会给各相关方造成巨大负担和不必要的资源浪费。

We think this saying needs to be discussed because it is not in conformity to the principle of "Law of non- retroactivity" . Meanwhile, it will result to huge burden to respective parties and unnecessary waste of resources.

因此，我们恳请贵方考虑对过渡期产品采用历史通行原则，明确对 2016 年 6 月 1 日之前已完成全部临床试验机构伦理审批的临床试验允许依照旧法规的要求执行。

Therefore, we ask your kind consideration of adopting the general practice for products in the transition period, and make clear that the old regulation should be applied to all applications with all clinical trials completed and approved by the Ethics institutions before June 1, 2016.

1. 一年内产品注册检验合格报告认定截止点的问题 Issue of time point of product registration test report within one year

“规范”提到临床前研究必须完成“一年内产品注册检验合格报告”，但是没有明确给出“临床试验开展日期”的定义。在实际操作和相关培训中，不同的部门给出了几种不同的解读。例如：“方案签署日期”、“伦理委员会批准日期”、“药监局备案日期”、“合同签署日期”、“第一例患者入组日期”、“最后一个机构协议或合同截止点”等。而“最后一个机构协议或合同截止点”是目前最常听到的说法。然而，这种说法在实际操作中存在一定问题。

The new GCP mentioned that “product registration Test Report within one year” must be completed for the pre-clinical research. However, no clear definition was given on “the date of conducting the clinical trial”. In actual practice and related trainings, numerous interpretations were given by different agencies, such as “date of signing the clinical trial scheme”, “date of "approval by the ethic committee”, “date of filing by CFDA”, “date of contract signing”, “date of the first patient enrolled”, “date of the

agreement or contract signing by the last institution", etc. Among the above interpretations, the last one is frequently heard recently, but it may cause some problems in actual practice.

通常，申办者从拿到合格的产品注册检验报告后到最后一家机构签署合同，必须经过一系列审批流程。现将流程按时间顺序列出如下：

Normally, the applicant has to go through a series of approval procedures for obtaining the product test report before the contract is signed. Timewise, the following procedures are shown below:

牵头单位伦理委员会审批（3 至 4 个月）；Approval of leading organization's ethic committee (3-4 months)

其他全部临床试验机构伦理委员会审批（2 至 6 个月）Approval by the ethic committee of all the other clinical trial institutions' ethic committee (2-6 months)

- 药局备案（5 至 10 个工作日）或三类器械临床审批（68 个工作日）CFDA's filing (5-10 work days) or approval of clinical trials for Class III devices (68 work days)
- 临床试验机构提交上级单位人类遗传资源国际合作项目申报（1 至 2 个月）Clinical trial institution to submit application for approval to the higher-level Human Resource International Cooperation Project （1-2 months）
- 科技部人类遗传资源办公室项目审查及批准（4 个月）Evaluation and approval by the Human Inheritage Resource Office of MOST (4 months)
- 牵头单位及其他临床试验机构审查以上审批结果及合同签署（1 至 2 个月）

Leading organizations and other clinical trial institutions evaluating the above approval result and contract signing (1-2 months)

从以上流程可以看出，以最后一家机构签署合同或协议为一年期考核终点，即使能到总局备案，最快也需要约 11 个半月才能完成。如果产品是属于总局 2014 年第 14 号中规定的创新的在中国未上市三类临床试验，则无论如何也无法合规地在一年内完成全部过程，最快也要 14 个半月。此外，如果在上述过程中遇到任何询问和讨论（例如伦理委员会或总局器械审评中心对申办者提出问题并要求解释）或临床研究机构接待各方面的审核所导致合同签署延期，都会超出一年的时限。这种现象在实际工作中较为常见，并非申办者资料准备不全所致，其进程也并非申办者所能控制。

The above flow chart shows that the shortest time is more than 11.5 months provided that the last institution signs the contract within one year period and filing is approved by CFDA. If the product is defined in CFDA's Order 14 of 2014 as Class III innovative and not marketed in China market, the shortest time is 14.5 months, no way to complete all procedures in compliance with the regulation within one year. Besides, the time will exceed the one-year period if there is any questions raised for the applicants to answer or discussions needed (for example the ethic committee or CMDE). This is quite frequent in reality but not as a result of the applicant that have not provided insufficient materials and it process is not under the applicant's control.

另外，“规范”的第八章“记录与报告”中第 82 条已经明确了申办者应当记录临床试验的相关信息的内容，其中包括“与临床试验机构签订的协议”。因此，我们郑重建议将协议的签署日期视为“试验的进行”的时间，而不是“试验前”的时间。

In addition, in article 82 "record and report"in Chapter 8 of the new China GCP, it is clear that the applicant has to record related information about clinical trial including "signed contract in relate to the clinical trial institutions". Therefore, we strongly recommend to take the date of agreement signing as the time for "clinical trial conducting", rather than the time of "pre-clinical trial".

当企业和临床试验机构共同对方案进行了认定，并通过了临床试验机构的伦理审查，就意味着试验从这个阶段进入了“开展”阶段，相关的临床资源和各种记录就开始受到临床试验的各种约定和约束。因此，我们认为牵头单位伦理委员会提交或通过的时间更适合作为注

册检测报告一年有效期的界定终点，这样更便于临床试验机构操作。即申办者应当在提交牵头单位的伦理申请时，提交一年期内的检测报告予以审查。

Once the company and the clinical trial institution have joint certification of the scheme and passed clinical trial ethic approval, the clinical trial enters into "conducting" stage and all related clinical resources and records will start to be committed and constraint. Therefore, we think the time of ethic committee submission or approval is a good time defined as the one-year period point, which is easier to operate by the clinical trial institutions. In other words, the applicant should submit their one-year test report for review while submitting the leading organization's ethic application.

我们完全理解总局和卫计委对一些单位将被淘汰或不符合中国最新国行标的产品引入临床试验对患者造成不良影响的忧虑，担心他们要求检测所在一年后不经检测重新出具同样的报告仅签署不同日期的做法，但这并不能从根本上解决问题。我们建议在上述明确界定后，可以要求申办者在新的国行标实施以后，在限定时间内提交新的符合国行标的检验报告予以备案和核查，以确保对患者的最大保护。同时在产品自身性能安全均无改变，亦无新的国行标发布实施的前提下，在原临床试验机构中进行的补充临床试验，不再要求提交更新后（即一年有效期内）的检测报告。

We fully understand that CFDA and NHFPC's concerns over the influence to the patients as a result of some out-of-date or non-conformity with the national or industry standard products and further concerns of getting the same report a year later with a new date without real test. However， this can still not be resolved by this way. We suggest that once the above is clearly defined, the applicant can be required to provide available within certain period of time the test report in conformity to the new national or industry standard thus to ensure the safety of the patients.

同时在产品自身性能安全均无改变，亦无新的国行标发布实施的前提下，在原临床试验机构中进行的补充临床试验，不再要求提交更新后（即一年有效期内）的检测报告。

Meanwhile, in the premise of no change in product safety performance nor issuance of new national or industry standard, the complement clinical trial conducted

in the original institution is no longer to be required to submit the updated (i.e. within one year period) inspection report.

另外，当临床研究涉及组合产品，需递交多个检测报告的时候，请明确应以哪份检测报告时限为准，以便于企业制定临床研究计划。

In addition, when multiple test reports are required to be submitted for the clinical research of combination products, please clarify which test report should be taken as the timeline to allow companies to make clinical research scheme.

2. 关于与多中心试验相关的问题：multi-center trial issue

1）多中心试验由牵头单位集中对数据进行管理和分析的问题 issue of leading party on multi-center trial's data management and analysis collectively

“规范”要求“各临床试验机构试验数据有关资料应当由牵头单位集中管理与分析”。按“规范”要求：“申办者负责发起、申请、组织、监查临床试验，并对临床试验的真实性、可靠性负责”。因此，申办者应对临床试验的数据管理和统计分析负责，并选择适合的机构开展此类工作。临床试验机构的主要职责应是按试验方案开展临床试验确保试验数据的真实和准确，并确保受试者安全；而开展数据管理和统计分析的工作超出了多数临床试验机构的现有能力，也不能确保临床试验数据和结果的客观和有效，且相应试验结果和分析难以被国际公认标准所接受。因此，我们建议临床试验的数据管理和统计分析仍然应由申办者委托独立于参与临床试验人员之外的、有相关经验或资质的机构或人员开展。

The new GCP requires that “relevant document of the clinical trial institution's experimental data and analysis shall be centrally managed by leading units. According to the Specification requirements, the sponsor is responsible for launching, applying, organizing, and monitoring clinical trials, and responsible for authenticity and reliability of clinical trial. Therefore, the sponsor is responsible for data management and statistical analysis of clinical trials and select appropriate institutions to carry out, The key responsibilities of a clinical test institution shall be in

accordance with the trial scheme to conduct clinical trials to ensure the test data true and accurate, and guarantee the safety of the participants for trial. However, data management and statistical analysis is beyond the current capability of most of the clinical trial institutions. It is hard to ensure all the clinical trial data and results are objective and effective, and the corresponding experimental results and analysis are difficult to be accepted by the standards recognized internationally. Therefore, we suggest that the clinical trial data management and statistical analysis be done by sponsor authorized institutions and individuals with qualifications and experience independent from the clinical trial participants,.

2）多中心临床研究的伦理审查 multi-center clinical research ethical review

“规范”第三十四条，“多中心临床试验的伦理审查应当由牵头单位伦理委员会负责建立协作审查工作程序，保证审查工作的一致性和及时性。各临床试验机构试验开始前应当由牵头单位伦理委员会负责审查试验方案的伦理合理性和科学性，参加试验的其他临床试验机构伦理委员会在接受牵头单位伦理委员会审查意见的前提下，可以采用会议审查或者文件审查的方式，审查该项试验在本临床试验机构的可行性，包括研究者的资格与经验、设备与条件等，一般情况下不再对试验方案设计提出修改意见”。此条规定削弱了伦理委员会对受试者的保护作用。目前所有的临床试验机构都有独立的伦理委员会，各机构以伦理会议的方式独立审核试验方案及相关资料，多家中心虽会产生不同的审核意见，但实质上是在更大范围内保证了方案的科学性和伦理性，对受试者的保护也更加全面。我们建议取消牵头单位的先行审核，而是参加试验的研究机构伦理委员会各自开展伦理审核，从而真正有效地实施在临床研究中对受试者的保护。

Item 34 of the new GCP says, “the ethical review of multicenter clinical trial shall be led by the unit of ethics committee that is responsible for establishing collaborative review procedures, to ensure the consistency and timeliness of the review. Before each test institution stats the clinical test, the lead unit ethics committee is responsible for inspecting the ethics plan of clinical trials rational and scientific. Under the

premise of ace[tong ethics committee review opinions ,the ethics committee of other participating institutions can examine the feasibility of the trial including the researcher's qualification and experience, equipment and conditions by way of conference review or documentation. In normal cases, no revised opinions will be proposed on the trial plan."

4. 各临床试验机构样本量及其分配 quantity of samples and allocations among various clinical trial institutions

在对"规范"的培训中，有关部门对两家临床试验机构进行临床试验的情况进行了解读，要求两家临床试验机构只能进行独立的临床试验，不能进行综合的统计分析考量。也就是说，在两家临床试验机构进行临床试验时，总的样本量（病例总数）应是多中心临床试验的两倍。

During recent training on China new GCP, relevant departments made explanation of the clinical test done by two clinical trials, requiring them to do clinical trials, but not make a comprehensive consideration of statistical analysis. In other words, the total sample size (cases) should be twice that of the multi-center clinical trial in these two clinical trial test units,

"规范"原文并未对临床试验的样本量（病例数）及其分配给出明确的指导。例如，目前已经发布的三类 X 射线审评指导原则虽对总的样本量（病例总数）有说明，但未明确在临床机构间进行分配的情况。在三类 X 射线审评指导原则中，明确组长单位合并所有中心的同一部位数据并出具统计分析报告。

The original text of the Specifications does not give clear guidance in sample size (number of cases) and its distribution of clinical trials.

我们认为，对总样本量（病例总数）的考量不应以参与临床试验机构的数量为基准，而应从统计分析的角度进行综合考虑，避免造成资源的浪费和将患者置于不必要的风险中。

We think that consideration of the total sample size (cases) should not be the benchmark for the number of institutions participating in clinical trials, but should be from the perspective of statistical analysis to avoid resources waste and unnecessary risk that might be brought to the patients.

5．临床试验基地的资质 Qualification of Clinical Trial bases

目前有大批临床试验基地的资质过期或者正在复核中，医疗器械临床试验基地不足。希望CFDA能快速审批临床试验基地资质的复核申请，使得有合理数量的资质基地供企业选择。

Currently, the qualification of a large number of clinical trial base is expired or under review, thus leading to insufficient number of clinical trial base for medical equipment. We hope CFDA give fast examination and approval to the application of qualified clinical trial base to provide companies to have reasonable number of clinical trial base to select.

此外，考虑到短期内临床试验基地紧缺的现状，如果该医院正在申请资质认定或者复核申请已经被受理，建议允许申办者选择此类医院开展临床试验。

In addition, considering the present situation of the shortage of clinical trial base in the short term, we suggest your permission of the sponsor to choose such hospitals for clinical trials if their applications for qualification authentication or review have already been accepted.

总之，由于“规范”现已处于执行阶段，而上述困惑或问题又无法得到监管机构的统一解答，因此很多会员企业对其今后是否能继续向中国引入最新医疗器械非常忧虑，均处于停滞和观望阶段。我们希望贵方对以上问题予以关注和重视，做好新旧法规之间的衔接工作，以减轻各方不必要的负担和资源浪费。如果需要任何更进一步的信息请随时与我们联系。

In summary, as the above confusion or problems are not resolved or answered by the regulating agencies during this new GCP implementing period, many of our

member companies are very concerned for whether or not to continue importing the newest medical equipment to China. They are at a wait-and-see stage. We hope to have your attention to the above issues and work better on the connection between the old and new regulations to reduce unnecessary burdens on all parties and waste of resources. Please contact us at any time if you need any additional information from us.

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此致

敬礼！

美国先进医疗技术协会（AdvaMed）
医疗影像及技术联盟（MITA）
美中贸易全国委员会（USCBC）
欧洲医学技术联盟,欧洲诊断制造商协会与欧洲医疗工业技术协会的联盟
(MedTech Europe)

2016 年 8 月 29 日