**Notice to sponsors on validation and qualification of computerised systems used in clinical trials**

**临床试验用计算机化系统的验证与确认**

Introduction:

介绍:

The integrity, reliability and robustness of data generated in clinical trials, e.g. data submitted to support marketing authorisation applications (MAAs), are essential to regulators. Most clinical trial data supporting MAAs are now collected through computerised data collection tools, e.g. electronic case report forms (eCRFs) and electronic patient reported outcomes (ePROs). In addition, a wide range of computerised media and systems are used in the conduct of a trial, such as safety databases, systems for electronic interactive response technology (eIRT), clinical trial management systems (CTMSs) etc., the use of which will increase in the future.

临床试验所产生数据，例如为支持上市许可申请(MAAs)而提交的数据，其完整性、可靠性和稳健性对监管机构至关重要。目前，大多数支持MAA（上市许可申请）的临床试验数据都通过计算机化数据收集工具收集，例如电子病例报告表（eCRF）和电子患者报告结果（ePROs）。此外，在进行试验时还使用了广泛的计算机化媒体和系统，如安全数据库、电子交互式响应技术系统（eIRT）、临床试验管理系统（CTMS）等，今后使用该系统还将增加。

Given recent inspection findings and the implications they have had on the integrity, reliability,robustness and acceptability of data in the context of MAAs, the GCP Inspectors Working Group (IWG) in cooperation with the Committee for Medicinal Products for Human Use (CHMP) sees the need to emphasize requirements for sponsors/vendors providing computerised systems or services as well as for the qualification and validation of computerised systems used to manage clinical trial data.

鉴于近期的检查缺陷，以及这些缺陷对MAA中数据的完整性、可靠性、稳健性和可接受性的影响，GCP检验员工作组与人用药品委员会（CHMP）合作，认为有必要对提供计算机化系统或服务的 申办人 /供应商以及用于管理临床试验数据的计算机化系统的确认和验证强调相关要求。

Legal and regulatory background:

法律法规背景:

* Directive 2001/20/EC, Article 2(l)
* 指令 2001/20/ec ，第 2(l) 条
* Directive 2005/28/EC, Article 7
* 指令 2005/28/ec ，第 7 条
* Regulation (EU) No 536/2014, Recital 51, Articles 2 (30), 2 (31), 47, 71
* 法令 (EU)No.536/2014 ，叙文 51 ，第 2(30) 条，第 2(31) 条，第 47 条 , 第 71 条
* ICH Guideline for good clinical practice E6(R2), (EMA/CHMP/ICH/135/1995 Revision 2) sections 1.65, 2.10, 2.13, 5.2.2, 5.5.3
* ICH E6(R2) 良好临床规范指南， (EMA/CHMP/ICH/135/1995 Revision 2) 第 1.65,2.10,2.13,5.2.2,5.5.3 节

Both Directive 2005/28/EC and Regulation (EU) No 536/2014 contain the provision that regardless whether a sponsor delegates all or part of the clinical trial related activities to an individual or an organization, the ultimate responsibility with regards to the clinical trial conduct — in particular related to the safety of subjects and the integrity, reliability and robustness of the data generated in the clinical trial — remains with the sponsor.

指令2005/28/EC和法令536/2014都载有一项规定，即无论 申办人将临床试验相关活动的全部或部分委托给个人或组织，对临床试验行为的最终责任——特别是与受试者的安全以及临床试验中生成数据的完整性、可靠性和稳健性——仍由 申办人承担。

The EU legal framework requires that the sponsor of a clinical trial and the investigator ensure that the clinical trial is conducted in accordance to the protocol and with the principles of GCP. Furthermore, the legislation also defines the process of GCP inspection by a competent authority and the coverage of such inspections. Finally, it contains provisions that the information generated should be recorded, handled and stored adequately for the purpose of ensuring effective inspection by Member States.

欧盟法律框架要求临床试验的申办人和研究员确保临床试验按照方案和GCP的原则进行。此外，法律还界定了主管当局对GCP检查的程序以及这种检查的涵盖范围。最后，还规定，应充分记录、处理和储存所生成的信息，以确保会员国进行有效检查。

**Validation and qualification of computerised systems:**

**计算机化系统的验证和确认:**

ICH E6(R2) requires that sponsors operating computerised trial data handling or computerised data systems, amongst others, shall validate these systems, maintain an audit trail for initial entry of data and any subsequent changes, maintain a security system to protect against unauthorized access and maintain a list of the individuals authorized to create, access, modify or delete data. Sponsors should set up these computerised systems in such a way that the blinding of clinical trials, when applicable, is maintained (ICH E6(R2), section 5.5.3). In addition, ICH E6(R2) requires that “systems with procedures that assure the quality of every aspect of the trials should be implemented” (section 2.13) and that “all clinical trial information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification” (section 2.10).

ICH E6（R2）要求 申办人进行计算机化试验数据处理或计算机化数据系统，此外，应验证这些系统，维护数据初始输入和任何后续更改的审计追踪，维护安全系统以防止未经授权的访问，并维护允许创建、访问、修改或删除数据的人员名单。 申办人应设置这些计算机化系统，以保持临床试验设盲（ ICH E6（R2），第5.5.3节）。此外，ICH E6（R2）要求"应实施"具有确保试验各个方面质量的程序的系统"（第2.13节），并"所有临床试验信息都应记录、处理和储存，使其能够准确报告、解释和核实"（第2.10节）。

Data integrity, reliability and robustness will depend on the design and the validation status of the computerised systems used. Failure to document and therefore demonstrate the validated state of a computerised system is likely to pose a risk to data integrity, reliability and robustness, which depending on the criticality of the affected data may result in a recommendation from the GCP inspectors to the CHMP not to use the data within the context of an MAA.

数据完整性、可靠性和稳健性将取决于所使用的计算机系统的设计和验证状态。未能记录并因此证明计算机系统的已验证状态可能会对数据完整性、可靠性和稳健性构成风险，这取决于受影响数据的重要性，可能导致GCP 检查员建议CHMP 不要在MAA 范围内使用数据。

The term qualification is used in this notice to describe verification of system functionality. The term validation is used to describe the process of establishing and documenting that the specified requirements of a computerised system can be consistently fulfilled from design until decommissioning of the system or transition to a new system (ICH E6(R2), section 1.65), i.e. it operates to defined specifications and defined procedures (SOPs) by a trained user.

此通知中使用术语“确认”来描述系统功能的确认。使用术语“验证”来描述确立和记录计算机化系统其特定要求，从设计到系统退役或过渡到一个新系统，可以始终如一地得到满足的过程(ICHE6(R2)，第1.65节)，例如，由经培训的用户按照既定的标准和程序（SOP）进行操作。

Lack of documentation (or access to documentation) of qualification activities:

缺乏确认活动的文件记录(或无法获得文件记录):

Recent inspection findings relating to the qualification and validation of computerised systems are of concern, as some sponsors have not been able to provide adequate documentation of the required qualification and validation activities for computerised data collection tools/software during inspections. Computerised systems used in clinical trials can be built by the sponsor but are more typically purchased from a vendor either under a license to use software or as part of a service purchased, which could also include e.g. trial specific builds, hosting of trial data, etc. Qualification activities would consequently be performed by the vendor, by the sponsor or by shared efforts.

近期，有关计算机系统的确认和验证的检查缺陷令人关切，因为一些 申办人未能在检查期间提供计算机数据收集工具 /软件所需的确认和验证活动的适当文件。临床试验中使用的计算机化系统可以由 申办人构建，但通常从供应商处购买，或根据使用软件的许可或作为所购买服务的一部分，包括特定试验的建立、试验数据的托管等。因此，确认活动将由供应商、 申办人或共同进行。

The sponsor is ultimately responsible for the validation of the computerised system and for providing adequate documented evidence on the validation process.

申办人对计算机化系统的验证，并提供有关验证过程的充分文件证据最终负责。

Sponsors shall be able to provide the GCP inspectors of the EU/EEA authorities with access to the requested documentation regarding the qualification and validation of computerised systems irrespective of who performed these activities.

申办方应能够向EU/EEA当局的GCP检查员提供所要求的关于计算机化系统的确认和验证的文件记录，不论这些活动由谁执行。

The sponsor may rely on qualification documentation provided by the vendor, if the qualification activities performed by the vendor have been assessed as adequate. However, the sponsor may also have to perform additional qualification (and validation) activities based on a documented risk assessment. The conditions for a sponsor to rely on a vendor's qualification documentation are described in Q&A # 9 on expectations regarding qualification documentation published on the EMA website:https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp

如果经评估认为供应商进行的确认活动是充分的，申办方可以依赖供应商提供的确认文件。否则，申办人可能需要根据书面的风险评估执行额外的确认(和验证)活动。申办方依赖供应商确认文件的条件详见EMA网站上公布的关于确认文件的期望问答9中有所描述:https://www.EMA.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp

If the sponsor choses to perform its own full qualification of a system purchased from a vendor, the sponsor should ensure access to the vendor’s system requirement specifications to perform its own appropriate qualification of the system. This is necessary, because otherwise the sponsor would not know all the built-in system functionalities and would consequently risk unknown functionalities/actions with unknown impact on their data. Considering the relevant version and configuration of a system, qualification and validation activities should be performed on the basis of all the requirement specifications the system was initially built on and any updates.

如果 申办人选择对从供应商处购买的系统完全由自己进行确认，则 申办人应确保可以访问供应商的系统需求规范，以自行执行系统的适当确认。这是有必要的，因为否则 申办人将不知道所有内置系统功能，因此会面临未知功能 /操作的风险，并对其数据产生未知影响。考虑到系统的相关版本和配置，应根据系统最初构建的所有需求规范及其任何更新执行确认和验证活动。

Insufficient contractual arrangements:

合同不充分:

Clear, written agreements should be in place to document any arrangements between the sponsor and the vendor with regards to qualification and validation. The sponsor remains responsible for ensuring that the conduct of the trial and the final data and data that are submitted to support an MAA comply with relevant legislation.

应签订明确的书面协议，说明 申办人和供应商之间关于确认和验证的任何事宜。 申办人还负责确保试验的进行和最终数据，以及支持 MAA 而提交的数据符合相关法律。

The GCP IWG has published Q&A # 8 regarding the pitfalls to be aware of regarding contractual arrangements with vendors of electronic systems used in clinical trials: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp

GCP IWG 发布了问答 8关于临床试验所用电子系统供应商合同事宜方面的应注意的常见错误：https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp

In the framework of a particular MAA, IT vendors could be inspected when they contractually assume clinical trial sponsor-related duties/activities and/or the contract between the sponsor and the vendor contains provisions for inspections/audits of duties/functions performed by the vendor.

在特定MAA 的框架内，当IT 供应商以合同方式承担与 申办人相关的临床试验责任 /活动，以及/或 申办人与供应商之间的合同包含供应商对检查 /审计应履行的职责/职能时，供应商可能也会被检查。

According to Article 2(l) of the Directive 2001/20/EC and Art 2.31 of Regulation (EU) No 536/2014, inspectors should be able to inspect third parties who have trial-specific relevant documentation. As qualification documentation of a generic software (a software without trial-specific functionalities or features) does not necessarily fall into this category, the sponsor should ensure access for GCP inspectors in case any such activities are delegated to the vendor, i.e. if the sponsor relies on the vendor for documentation of system requirement specifications, test documentation, etc.

根据指令2001/20/EC第2（l）条和法令（EU）536/2014第2.31条，检查员应能够检查具有特定试验相关文件的第三方。由于通用软件（没有试验相关功能的软件）的确认文件不一定属于此类别，因此，如果任何此类活动委托给供应商，如， 申办人依赖供应商的系统需求规范、测试文件等， 申办人应确保 GCP 检验员能够访问该文件。

It is not acceptable to use computerised systems in clinical trials for which the validation status is not confirmed or for which appropriate documentation on system validation cannot be made available to GCP inspectors.

在临床试验中，如果验证状态未得到确认，或者不能向GCP检查员提供有关系统验证的适当文件，则不能使用计算机化系统。

If appropriate contracts cannot be put in place, e.g. because a vendor does not allow provision of adequate measures as listed above (access to system requirements specifications, pre-qualification audits, access for GCP inspectors, etc.) and set out in Q&A # 8, systems fromsuch a vendor shall not be used in clinical trials. This is irrespective of the number of sponsors making use of or having used the systems, the number of years such systems have been on the market etc., as serious GCP non-compliances and risks to data integrity, reliability and robustness could exist unnoticed if auditors and GCP inspectors are not allowed access as well as if potential serious breaches are not escalated appropriately by the vendor.

如果无法制定适当的合同，例如，由于供应商不允许提供上述适当措施（获取系统需求规范、确认前审计、GCP 检验员查阅等），且在问答#8 中列出，此类供应商的系统不得用于临床试验。无论有多少 申办人使用或曾经使用过该系统、此类系统在市场上的年数等，如果不允许审计员和 GCP 检查员访问，以及如果潜在的严重缺陷未得到适当升级，则可能存在不易察觉的严重GCP 违规情况以及数据完整性、可靠性和稳健性风险。