安徽省药品审评查验中心

皖药审查生产〔2023〕69号

安徽省药品审评查验中心
药品GMP符合性检查告知书

安徽安科生物工程（集团）股份有限公司:

按照《药品管理法》《药品生产监督管理办法》的要求，药品审评查验中心于2023年02月20日至02月24日组织检查组对你单位的“治疗用生物制品（注射用人生长激素）”进行了药品GMP符合性检查（与药品生产许可合并检查），发现严重缺陷0项、主要缺陷0项、一般缺陷15项。经综合评定，“治疗用生物制品（注射用人生长激素）”的生产和质量管理符合《药品生产质量管理规范（2010年修订）》要求。

生产地址	生产车间	生产线	生产范围
合肥市高新区海关路4号	三号厂房	人生长激素原液三-1/2生产线	治疗用生物制品（注射用人生长激素）
		注射用人生长激素制剂三-3-2生产线	

特此通知。

附件：药品 GMP 符合性检查不合格项目情况

[注：注射用人生长激素（规格:4IU/1.33mg/支，药品批准文号：国药准字 S19990021）同时发生制剂生产场地和药品生产工艺（配制搅拌转速等）变更,企业应按照相关规范性文件和变更技术指导原则要求进行研究验证后确认变更管理类别，并根据变更管理类别进行补充申请、备案，获得批准、备案完成后方可生产上市]

安徽省药品审评查验中心

2023年8月9日

抄送：省局许可注册处、药品生产监管处、第一分局，省局领导。

安徽省药品审评查验中心　　2023 年 8 月 9 日印发

药品GMP符合性检查不合格项目情况

企业名称	安徽安科生物工程（集团）股份有限公司
检查范围	治疗用生物制品（注射用人生长激素）（三号厂房人生长激素原液三-1/2生产线、三号厂房注射用人生长激素制剂三-3-2生产线）

严重缺陷：未发现

主要缺陷：未发现

一般缺陷：15项

1.三-3-2注射用人生长激素制剂车间用于灌装过程检测澄明度的澄明度检测仪安装在轧盖间未进行可行性评估。（第56条）

2.三号厂房2楼GH纯化精制车间原液样品存放室内，合格和待检的原液分别存放在-20±5℃冰柜和冰箱中，温度如超标仅能室内蜂鸣报警，不能远程无线报警，无温度监测数据打印设施，仅在上下午各监测记录一次温度。（第71条）

3.部分同一设备名称不一致，如人生长激素纯化精制车间层析一室设备状态标识中设备名称为层析柱3，该设备使用记录中设备名称为离子交换层析（一）。（第87条）

4.2023年度计量计划中，未将箱式电阻炉、恒温水浴锅、培养箱等检验仪器所需校准的量程范围列入；LC20A高效液相色谱仪（设备编号：5211-38）每2年校准一次，企业未根据仪器的使用频率、老化程度等增加检验仪器期间核查频次，以保持对设备校准状态的可信度。（第90条）

5.部分确认存在不足：（1）三号厂房1楼纯蒸汽发生器（型号PSG1500/B，设备编号：C1114-CS-01）对同一时期车间多个设备同时使用纯蒸汽的供应能力未进行确认；（2）《自动进出料系统确认报告》（文件编号：SOR-QR-SB-C3-012）性能确认未进行动态悬浮粒子和浮游菌在线监测。（第140条）

6.部分文件内容存在不足：（1）《注射用人生长激素与人干扰素α2b制剂生产线共用部分生产区的风险评估报告》（文件编号：SOR-ZL-001-02-18）对于生产组织方式的风险降低措施为：1、两种产品不同时生产；2、减少不同产品同时生产的频率；3、只同一品种连续生产，采用阶段式生产方式。此风险降低措施存在矛盾，措施不明确；（2）《物料供应商评估、批准操作规程》（文件编号：SOP-ZG-005）与《供应商评估和批准管理制度》（文件编号：SMP-ZL-019）对供应商现场审计频

次规定不一致，如:《物料供应商评估、批准操作规程》规定“A 类物料供应商通过 GMP、GSP、ISO9000 认证企业可免于现场审计”，但《供应商评估和批准管理制度》规定“A 类物料供应商每两年进行一次现场审计”。(第 150 条)

7.部分批生产记录内容不全或数据不正确，如注射用人生长激素一级种子液(批号: 20220521D)合并记录中，合并完摇瓶灭菌记录中未记录脉动真空灭菌器设备编号; 制剂阶段，培养皿经 VHP 传递舱灭菌，未记录使用的过氧化氢的浓度、批号及灭菌结束通风后过氧化氢浓度降低到 1ppm 的时间; 药液配制岗位领料单中人生长激素原液批号填写错误，应填写混合批的批号，但错误填写为混合前的批号。(第 175 条)

8.《人生长激素原液质量标准》(文件编号: SMP-BZ-CP-020)中个别检验项目描述不规范，如等电聚焦描述为等电点，细菌内毒素描述为细菌内毒素含量。(第 221 条)

9.人生长激素原液(批号: P32-20220325)外源性 DNA 残留量检测时，未记录所使用的荧光定量 PCR 试剂盒、磁珠法提取 DNA 试剂盒的生产厂家及批号等信息; 人生长激素原液(批号: P32-20230205)总蛋白含量测定时，供试品 1 蛋白浓度计算为 21.89mg/ml，应为 21.95mg/ml，计算错误; 注射用人生长激素(批号: 20220513D)不溶性微粒检测时所用的微粒检查用水使用前未经不大于 1.0μm 的微孔滤膜滤过。(第 223 条)

10.《标准品、对照品管理规程》(文件编号: SOP-JC-GL-010)中未规定应定期查询并收集中国食品药品检定研究院发布的对照品停用通知的内容，以确保对照品使用的合规性。(第 227 条)

11.三-3-2 注射用人生长激素制剂车间灌装室(B 级)未根据空气净化系统确认结果和风险评估确定浮游菌和悬浮粒子的采样点位置。(无菌药品附录 第 10 条)

12.《三号厂房 3 层车间制剂灌装区空调净化系统确认报告》(文件编号: SOR-QR-SS-C3-003)的单向流流型确认，检查结果未确认“在层流罩四周发烟，无烟雾从层流罩外进入层流罩控制区域”。(无菌药品附录 第 33 条)

13.灯检岗位人员视力检查频次为每年一次，不符合中国药典三部《生物制品分包装及贮运管理》中灯检人员应每半年检测一次视力的要求。(无菌药品附录 第

79 条）

14.三号厂房取样间未按照《质量控制部洁净室清洁、消毒规程》（文件编号：SOP-JC-GL-006）要求每周进行一次清洁消毒，实际为取样前后进行清洁消毒。（取样附录 第 8 条）

15.EX125ZH 型准微量天平配置的天平打印机使用时，时间项的修改未按权限进行管理，使用人均可修改。（计算机化系统附录 第 14 条）

Anhui Provincial Drug Evaluation and Inspection Center

W. Y. S. C. S. C. [2023] No.69

Anhui Provincial Drug Evaluation and Inspection Center Notification of Drug GMP Compliance Inspection Results

To Anhui Anke Biotechnology (Group) Co., Ltd.:

In accordance with the requirements of the *Drug Administration Law* and the *Measures for the Supervision and Administration of Drug Production*, the Drug Evaluation and Inspection Center organized an inspection team to conduct a drug GMP compliance inspection on your manufactured "Therapeutic Biologics (Human Growth Hormone for Injection)" from February 20 to February 24, 2023, and it was found that there were 0 critical deficiency, 0 major deficiency, and 15 minor deficiencies. After comprehensive assessment, the production and quality management of "Therapeutic Biologics (Human Growth Hormone for Injection)" are in compliance with the requirements of the *Good Manufacturing Practice of Medical Products (2010 revision)*.

Production Address	Production Workshop	Production Line	Production Scope
Haiguan Road K-1, High & New Development Zone, No.669, West Changjiang Road, Hefei City	No.3 Plant	3-1/2 production line of Human growth hormone bulk solution	Therapeutic Biologics (Human Growth Hormone for Injection)
		3-3-2 production line of Human growth hormone for injection	

It is hereby notified.

Annex: Non-compliant Items in the Drug GMP Compliance Inspection

Anhui Provincial Drug Evaluation and Inspection Center

August 9, 2023

CC: Licensing and Registration Department, Drug Production Supervision Department, First Sub-Bureau, and Leadership of Anhui Medical Products Administration
Anhui Provincial Drug Evaluation and Inspection Center　　Printed and issued on August 9, 2023

Non-compliant Items in the Drug GMP Compliance Inspection

Enterprise Name	Anhui Anke Biotechnology (Group) Co., Ltd.
Inspection Scope	Therapeutic Biologics (Human Growth Hormone for Injection) (3-1/2 production line of Human growth hormone bulk solution and 3-3-2 production line of Human growth hormone for injection in No.3 Plant)

Critical deficiencies: 0 item

Major defects: 0 item

Minor defects: 15 items

1. The clarity tester used in the filling process of 3-3-2 human growth hormone for injection preparation workshop, was installed in the capping room without feasibility evaluation. (Article 56)

2. In drug substance samples storage room of GH purification and refining workshop on the second floor of No. 3 Plant are stored indoors, qualified DS and DS to be tested were stored in -20 ± 5 ℃ freezers and refrigerators respectively, if the temperature exceeds the standard, only indoor buzzing alarms can be triggered, but remote wireless alarms cannot be triggered. There was no temperature monitoring data printing facility, and only temperature monitoring and recording were conducted once in the morning and afternoon. (Article 71)

3. Some of the same equipment names were inconsistent, such as the equipment name in the chromatography room of the human growth hormone purification and refining workshop, which was chromatography column 3 in the equipment status label, and the equipment name in the equipment usage record was ion exchange chromatography (I). (Article 87)

4. In the 2023 annual measurement plan, the range of calibration required for inspection instruments such as box type resistance furnaces, constant temperature water baths, and incubators was not included; The LC20A high-performance liquid chromatography instrument (equipment number: 5211-38) is calibrated every 2 years. The company did not increase the frequency of QC instrument check during the use and aging of the instrument to maintain the credibility of the equipment calibration status. (Article 90)

5. Partial qualification has shortcomings: (1) The pure steam generator (model PSG1500/B, equipment number C1114-CS-01) on the first floor of No.3 Plant has not been confirmed for its ability to supply pure steam to multiple equipment in the same workshop during the same period; (2) The performance qualification report of the automatic feeding and discharging system (document number: SOR-QR-SB-C3-012) was not subjected to online monitoring of dynamic suspended particles and planktonic bacteria. (Article 140)

6. Some of the documents have shortcomings: (1) Risk assessment report on the shared production area of the production line for human growth hormone for injection and human interferon alpha 2b for injection (document number: SOR-ZL-001-02-18). The risk reduction measures for the production organization method: 1. The two products are not produced at the same time; 2. Reduce the frequency of simultaneous production of different products; 3. Continuous production of the same variety using a staged production method. The risk reduction measures were contradictory and unclear; (2) The Operating Procedures for Material Supplier Evaluation and

Approval (document number: SOP-ZG-005) and the Supplier Evaluation and Approval Management System (document number: SMP-ZL-019) have inconsistent regulations on the frequency of supplier on-site audits. For example, the Operating Procedures for Material Supplier Evaluation and Approval stipulate that "A-class material suppliers who have passed GMP, GSP, and ISO9000 certifications are exempt from on-site audits", while the Supplier Evaluation and Approval Management System stipulates that "A-class material suppliers undergo on-site audits every two years". (Article 150)

7. Part of the batch production records have incomplete content or incorrect data, such as in the merged record of human growth hormone for injection grade I seed solution (batch number: 20220521D), the equipment number of the pulsating vacuum sterilizer was not recorded in the merged shake bottle sterilization record; In the preparation stage, the culture dish was sterilized through VHP transfer chamber, without recording the concentration and batch number of hydrogen peroxide used, and the time when the hydrogen peroxide concentration decreases to 1ppm after ventilation after sterilization is completed; The batch number of human growth hormone bulk solution in the material requisition form for the drug preparation position was filled in incorrectly. The batch number of the mixed batch should be filled in, but the incorrect filling was the batch number before mixing. (Article 175)

8. The specification of human growth hormone bulk solution (document number: SMP-BZ-CP-020) does not provide standardized descriptions of individual test items, such as isoelectric focusing was described as isoelectric points and bacterial endotoxin content was described as bacterial endotoxin. (Article 221)

9. During the detection of exogenous DNA residue in human growth hormone bulk solution (batch number: P32-20220325), the manufacturer and batch number of the fluorescent quantitative PCR kit and magnetic bead DNA extraction kit used were not recorded; When measuring the total protein content of human growth hormone bulk solution (batch number: P32-20230205), the protein concentration of test substance 1 was calculated to be 21.89mg/ml, which should be 21.95mg/ml, and the calculation was incorrect; The particle inspection water used for the detection of insoluble particles in human growth hormone for injection (batch number: 20220513D) has not been filtered through a microporous membrane of no more than 1.0um before use. (Article 223)

10. The Management Regulations for Standard and Reference Substance (document number: SOP-JC-GL-010) did not specify that regular inquiries and collection of reference material discontinuation notices issued by the China Food and Drug Control Research Institute should be conducted to ensure compliance with the use of the reference. (Article 227)

11. The filling room (Level B) of the human growth hormone for injection preparation workshop (3-3-2) did not determine the sampling points for planktonic bacteria and suspended particles based on the confirmation results of the air purification system and risk assessment. (Article 10 of the Appendix for Sterile Drugs)

12. The one-way flow pattern confirmation of the air conditioning purification system in the formulation filling area of the 3rd floor workshop of No. 3 Plant (document number: SOR-QR-SS-C3-003) did not confirm that "smoke was emitted around the laminar flow hood, and no smoke entered the laminar flow hood control area from outside the hood". (Article 33 of the Appendix for Sterile Drugs)

13. The frequency of visual acuity testing for lamp inspection personnel is once a year, which did not comply with the requirement of semi annual visual acuity testing for lamp inspection

personnel in Volume III of the Chinese Pharmacopoeia "Packaging and Storage Management of Biological Products". (Article 79 of the Appendix for Sterile Drugs)

14. The sampling room of No. 3 Plant did not follow the requirements of the Quality Control Department's Cleanroom Cleaning and Disinfection Regulations (document number: SOP-JC-GL-006) for cleaning and disinfection once a week. In reality, cleaning and disinfection were carried out before and after sampling. (Article 8 of the Appendix for Sampling)

15. When using the balance printer of the EX125ZH quasi micro scale configuration, the modification of time items was not managed according to permissions, and users can make modifications. (Article 14 of the Appendix for Computerized System)