# Guidance for Industry

## Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production

**U.S. Department of Health and Human Services**

**Food and Drug Administration**

**Center for Drug Evaluation and Research (CDER)**

**October 2006**

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# Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production

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**U.S. Department of Health and Human Services 美国卫生和福利部**

**Food and Drug Administration 食品药品管理局**

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.
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## I. INTRODUCTION 介绍

This guidance for industry provides the Agency's current thinking on how to evaluate out-of-specification (OOS) test results. For purposes of this document, the term *OOS results* includes ***all*** test results that fall outside the specifications or acceptance criteria established in drug applications, drug master files (DMFs), official compendia, or by the manufacturer. The term also applies to all in-process laboratory tests that are outside of established specifications.[2] 本指南旨在表达当局对如何评价OOS结果的最新想法。本文件中OOS结果这个术语包括所有不符合质量标准，或经由药品申请、DMF文件、官方药典及生产商所确立的可接受标准的检测结果。这个术语也适用于所有不符合已建立标准的中控化验室检测结果。

This guidance applies to chemistry-based laboratory testing of drugs regulated by CDER. It is directed toward traditional drug testing and release methods. These laboratory tests are performed on active pharmaceutical ingredients, excipients and other components, in-process materials, and finished drug products[3] to the extent that current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211) and the Federal Food,

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[1] This guidance has been prepared by the Office of Compliance/Division of Manufacturing and Product Quality in the Center for Drug Evaluation and Research (CDER).本指南由药品评审中心 CDER 生产和产品质量分部法规符合办公室起草。

[2] In certain instances, in-process testing is done solely for purposes of triggering real time equipment or system adjustments to prevent process drift. This guidance does not address these situations. 在特定情况下，中控检测的目的仅仅是触发实时设备和体系调节以防止工艺偏差。本指南不适用于这种情况。

[3] Chemistry-based laboratory testing of biotechnology products that are under the jurisdiction of CDER are within the scope of this guidance. However, this guidance is not intended to address biological assays (e.g., in vivo, immunoassays). 由 CDER 负责的生物技术产品的化学检测项目在本指南范围内。但本指南不适用于生物含量检测（例如体内免疫检测）。

Drug, and Cosmetic Act (the Act) (section 501(a)(2)(B)) apply. The principles in this guidance also apply to in-house testing of drug product components that are purchased by a firm. This guidance can also be used by contract firms performing production and/or laboratory testing responsibilities. Specifically, the guidance discusses how to investigate OOS test results, including the responsibilities of laboratory personnel, the laboratory phase of the investigation, additional testing that may be necessary, when to expand the investigation outside the laboratory, and the final evaluation of all test results. 本指南适用于由CDER管理的药品类别的化学实验室。它直接针对传统的药品测试和放行方法。这些实验室检测项目是对活性药物成份、赋形剂和其它组件、中控材料和制剂成品，这些就是CGMP法规（21CFR210部分和211部分）和联邦食品药品和化妆品法案（501(a)(2)(B)）所适用的范围。本指南的公司采购的用于制剂成品的组件在公司内的检测。本指南也能用于承担生产和/或实验室测试的合同公司，尤其是，指南讨论如何调查OOS结果时，包括实验室人员职责，化验室调查阶段、可能需要的附加测试、何时扩大调查至化验室之外，和所有检测结果的最终评价。

The Agency, in accordance with its August 2002 “Pharmaceutical CGMPs for the 21st Century” initiative, encourages modern approaches to manufacturing, monitoring, and control to enhance process predictability and efficiency. Process Analytical Technology (PAT) takes a different approach to quality assurance by using process controls and in-process data as the release specification instead of relying on single laboratory determinations to make batch acceptability decisions. This guidance is not intended to address PAT approaches, as routine in-process use of these methods might include other considerations. For information on timely in-process testing, see the CGMP guidance entitled *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.* 官方机构，按照2002年8月“21世纪药品CGMPS”倡导的，鼓励采用现代方法制造、监测和控制以提高工艺可预测性和效率。工艺分析技术（PAT）采用了不同的质量保证方法，即采用工艺控制和制程数据作为放行标准而不仅信赖于单一的化验室检测来作出批放行决定。由于这些方法的用于常规制程可能还有其它考虑，本指南并准备对PAT方法进行探讨。关于即时制程检测，参见CGMP指南 *PAT---药品研发、生产和质量保证框架。*

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required. FDA的指南文件，包括本指南，并不具备法规强制性。指南仅是用于表述当局的目前对某个问题的看法，应该当作一种推荐来采纳，除非在其中引用了特定的法规要求。在官方指南中，SHOULD表示建议或推荐的方法，并非必须。

## II. BACKGROUND 背景

Laboratory testing, which is required by the CGMP regulations (§§ 211.160 and 211.165), is necessary to confirm that components, containers and closures, in-process materials, and finished products conform to specifications, including stability specifications. cGMP法规（211章第160部分和211章第165部分）要求化验室对药品的成分、包装材料、过程控制及成品进行检测，确保其达到既定的标准要求，包括稳定性标准要求。

Testing also supports analytical and process validation efforts.[4] General CGMP regulations covering laboratory

[4] Specifications must be scientifically sound and appropriate (§ 211.160(b)), test procedures must be validated as to their accuracy, sensitivity, specificity, and reproducibility (§ 211.165(e)), and the suitability of the test procedures under actual conditions of use must be documented (§ 211.194(a)(2)). For products that are the subjects of new drug applications (NDAs), abbreviated new drug applications (ANDAs), or investigational new

operations can be found in part 211, subparts I (Laboratory Controls) and J (Records and Reports). These regulations provide for the establishment of scientifically sound and appropriate specifications, standards, and test procedures that are designed to ensure that components, containers and closures, in-process materials, and finished drug products conform to the established standards. Section 211.165(f) of the CGMP regulations specifies that finished drug products that fail to meet established standards, specifications, or other relevant quality control criteria will be rejected. 检验亦应支持方法验证和工艺验证。通用CGMP规范包括化验室操作，在211部分章节 I (化验室控制) 和J (记录和报告)可以查阅到。这些法规用于建立科学合理和适当的质量规格、标准和检验方法，用于保证组件、容器和密闭器材、中控材料和制剂成品符合既定标准。CGMP法规211部分165（f）指出制剂成品不符合既定标准、规格或其它相应质量控制标准时应拒绝放行。

Both finished pharmaceuticals and active pharmaceutical ingredients (APIs) are to be manufactured in accordance with current good manufacturing practice under section 制剂成品和原料药（APIs）生产均应符合现行GMP对应条款下的要求。

501(a)(2)(B) of the Act. Current good manufacturing practice for APIs includes the performance of scientifically sound raw material testing, in-process monitoring, release and stability testing, process validation, and adequate investigations of any OOS result obtained from such testing. All citations to part 211 in this document pertain to finished pharmaceuticals, but these referenced regulatory requirements are also consistent with Agency guidance on CGMPs for APIs with respect to laboratory controls, which include out-of-specification investigations. See FDA's guidance for industry *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (ICH Q7A) for specific recommendations.[5] 法案的501（a）(2)(B)中对原料药（API）的CGMP包括科学合理的原料检测、中控监测、放行和稳定性测试、工艺验证和对任何来自于这些测试的OOS结果的充分的调查。本文中所有对CFR211章的引用都涉及制剂产品，但这些相关法规要求也与当局对原料药实验室控制方面的要求一致，其中包括OOS调查。参见FDA行业指南：Q7A活性药物成份优良生产规范指南（ICH Q7A）特定推荐.

The responsibility of a contract testing laboratory in meeting these requirements is equivalent to that of a manufacturing firm. 对合同化验室的要求与对生产公司的化验室要求相同。

## III. IDENTIFYING AND ASSESSING OOS TEST RESULTS界定和评价OOS检验结果—PHASE I: LABORATORY INVESTIGATION第一步：化验室调查

FDA regulations require that an investigation be conducted whenever an OOS test result is obtained (§ 211.192).[6] The purpose of the investigation is to determine the cause of the OOS result. The source of the OOS result should be identified either as an aberration of the measurement process or an aberration of the

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drug applications (INDs), specifications are contained in the application or DMF. Specifications for nonapplication products may be found in official compendia or established by the manufacturer. 制订的标准应科学合理并恰当（211章第160部分b），检测方法应经过验证，验证应包括准确度、灵敏度、专属性及重复性（211章165部分e），测试时所做的系统适用性试验数据应记录（211章194部分a（2））。对于新药申请（NDA）、仿制新药申请（ANDA）和研究用新药申请（IND）的药品，其质量标准应包括在申报文件或DMF文件中。非申请项目的药品的质量标准应为公定标准或生产厂商自建标准。

[5] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/cder/guidance/index.htm. 我们定期更新各指南。为保证使用最新版本的指南，请至 http://www.fda.gov/cder/guidance/index.htm 访问CDER指南页。

[6] Although the subject of this document is OOS results, much of the guidance may be useful for examining results that are out of trend.虽然本文的主题是 OOS 结果，指南内许多内容对于检查偏离趋势结果亦有帮助。

manufacturing process. Even if a batch is rejected based on an OOS result, the investigation is necessary to determine if the result is associated with other batches of the same drug product or other products. Batch rejection does not negate the need to perform the investigation. The regulations require that a written record of the investigation be made, including the conclusions and follow-up (§ 211.192). FDA法规要求当发现OOS结果时应立即展开调查。调查的目的是确定引起OOS的原因。应确定是检验过程的异常还是生产工艺异常导致的OOS结果。即使因OOS结果判定了不合格的批，仍必须进行调查以确定该结果是否影响到同种产品其它批号或其它产品，一批不合格也不能否定调查的必要。法规(§ 211.192)要求要有调查的书面记录，包括结论和跟进措施。

To be meaningful, the investigation should be thorough, timely, unbiased, well-documented, and scientifically sound. The first phase of such an investigation should include an initial assessment of the accuracy of the laboratory's data. Whenever possible, this should be done before test preparations (including the composite or the homogenous source of the aliquot tested) are discarded. This way, hypotheses regarding laboratory error or instrument malfunctions can be tested using the same test preparations. If this initial assessment indicates that no meaningful errors were made in the analytical method used to arrive at the data, a full-scale OOS investigation should be conducted. For contract laboratories, the laboratory should convey its data, findings, and supporting documentation to the manufacturing firm’s quality control unit (QCU), who should then initiate the full-scale OOS investigation. 为了使调查有意义，调查应是彻底的，及时的，没有偏见的，形成文件并经得起科学推敲。调查的第一阶段应包括对实验室数据的准确性的初步评价。如果可能，这应在丢弃试验溶液（包括被测样品复合的或同质的来源）之前进行。这样，假定是实验室错误或仪器故障，可以使用原溶液测定。如果初步评估显示在得到该数据的分析过程中没有生错误，应进行全面的OOS调查。如果OOS结果出自合同化验室，化验室应将数据、所有发现和支持性文件提交生产商的质量部门，以便其展开全面的OOS调查。

**A. Responsibility of the Analyst 化验员职责**

The first responsibility for achieving accurate laboratory testing results lies with the analyst who is performing the test. The analyst should be aware of potential problems that could occur during the testing process and should watch for problems that could create inaccurate results. 得到精确的化验结果的责任首先是在做检验的化验员身上。化验员应明白检验过程中可能会产生的问题，对可能会导致不准确结果的问题应特别注意。

In accordance with the CGMP regulations in § 211.160 (b)(4), the analyst should ensure that only those instruments meeting established performance specifications are used and that all instruments are properly calibrated. 依照第211章160部分（b）（4）中cGMP的要求，化验员应确认只使用那些符合性能要求并经过正确校正的仪器。

Certain analytical methods have system suitability requirements, and systems not meeting these requirements should not be used. For example, in chromatographic systems, reference standard solutions may be injected at intervals throughout chromatographic runs to measure drift, noise, and repeatability. If reference standard responses indicate that the system is not functioning properly, all of the data collected during the suspect time period should be properly identified and should not be used. The cause of the malfunction should be identified and, if possible, corrected before a decision is made whether to use any data prior to the suspect period. 特定的分析方法有系统适用性要求，如果系统不符合这些要求则不能用于该检验。例如，在色谱系统中，对照液可能在色谱运行过程中进针以测试其飘移、噪声和重复性。如果对照品响应显示系统功能不适用，所有在可疑时间段收集的数据应适当鉴别且不能采用。故障原因应该查出，并且如果可能的话，在决定是否采用可疑时间段之前的任何数据前应采取纠正措施。

Analysts should check the data for compliance with test specifications before discarding test preparations or standard preparations. When unexpected results are obtained and no obvious explanation exists, test preparations should be retained, if stable, and the analyst should inform the supervisor. An assessment of the accuracy of the results should be started immediately. 分析员在丢弃供试样和标准样前，应该检查数据是否符合检测标准。如果出现结果不在预期内，且没有明显的解释，如果供试液稳定的话应该保留，分析员应该通知主管。对结果准确性的评估应立即开始。

If errors are obvious, such as the spilling of a sample solution or the incomplete transfer of a sample composite, the analyst should immediately document what happened. Analysts should not knowingly continue an analysis they expect to invalidate at a later time for an assignable cause (i.e., analyses should not be completed for the sole purpose of seeing what results can be obtained when obvious errors are known). 如果错误是明显的，例如样品溶液溅出或样品成分转移不完全，分析员应立即记录下发生的事情。分析员在明知这类错误的前提下，不应继续分析过程，而在后来将结果根据该可归结的原因判定无效（即如果有已知明显错误存在时，不应该仅为了看看会出来什么结果而继续检验）。

**B. Responsibilities of the Laboratory Supervisor化验室主管职责**

Once an OOS result has been identified, the supervisor's assessment should be objective and timely. There should be no preconceived assumptions as to the cause of the OOS result. Data should be assessed promptly to ascertain if the results might be attributed to laboratory error, or whether the results could indicate problems in the manufacturing process. An immediate assessment could include re-examination of the actual solutions, test units, and glassware used in the original measurements and preparations, which might provide more credibility for laboratory error hypotheses. 对 OOS 结果进行确认，主管对可能的原因进行客观及时的评估，不应预先假想 OOS 结果的原因。应迅速评价数据以确定结果是因为实验室错误，还是表明了生产工艺有问题。直接的评估可以包括对目前溶液，检验单位，最初测量和准备使用的玻璃器具的复验。复验可能提供对实验室错误假定的更多的可信性。

The following steps should be taken as part of the supervisor's assessment: 主管的评估应包括以下步骤

1. Discuss the test method with the analyst; confirm analyst knowledge of and performance of the correct procedure. 与化验员讨论检验方法，确认化验员的经验和能正确使用方法的能力

2. Examine the raw data obtained in the analysis, including chromatograms and spectra, and identify anomalous or suspect information. 检查原始分析中得到的记录，包括谱图等，确定有无异常和可疑信息。

3. Verify that the calculations used to convert raw data values into a final test result are scientifically sound, appropriate, and correct; also determine if unauthorized or unvalidated changes have been made to automated calculation methods. 确认原始数据计算方法的科学合理性、恰当性和正确性，确认自动计算方法是否有被擅自改动。

4. Confirm the performance of the instruments. 检查仪器的性能；

5. Determine that appropriate reference standards, solvents, reagents, and other solutions were used and that they met quality control specifications. 检查标准品、试剂、溶剂和其它用到的溶液，应满足质量控制的要求。

6. Evaluate the performance of the test method to ensure that it is performing according to the standard expected based on method validation data and historical data. 对检验方法的性能进行评价以保证其性能符合基于方法验证数据和历史数据而期望得到的表现。

7. Fully document and preserve records of this laboratory assessment. 保存该化验室评价的所有文件和记录。

The assignment of a cause for OOS results will be greatly facilitated if the retained sample preparations are examined promptly. Hypotheses regarding what might have happened (e.g. dilution error, instrument malfunction) should be tested. Examination of the retained solutions should be performed as part of the laboratory investigation.如果马上检查保留的样品，将会使OOS结果原因的陈述容易得多，可验证可能发生事故的假设（如稀释错误、设备故障等）检查保留的溶液应作为实验室调查的一部分。例：

*Examples*: 例如

Solutions can be re-injected as part of an investigation where a transient equipment malfunction is suspected. Such hypotheses are difficult to prove. However, reinjections can provide strong evidence that the problem should be attributed to the instrument, rather than the sample or its preparation. 如果怀疑是瞬时的仪器故障，作为调查的一部分，可以重新进样。很难证明这些假想。尽管如此，再次进样强有力的证明了是仪器的原因而不是样本或其它的制备的原因。

For release rate testing of certain specialized dosage form drugs that are not destroyed during testing, where possible, examination of the original dosage unit tested might determine whether it was damaged during laboratory handling in a way that affected its performance. Such damage would provide evidence to invalidate the OOS test result, and a retest would be indicated. 对于特定剂型的药物，在检验中没有破坏的释放速率的试验，如果可能，对最初检验的剂量单位的检查，可能确定它是否在实验室处理中以影响它性能的方式被破坏了。这样的破坏能够证明OOS检验结果无效，表明应复验。

Further extraction of a dosage unit, where possible, can be performed to determine whether it was fully extracted during the original analysis. Incomplete extraction could invalidate the test results and should lead to questions regarding validation of the test method. 如果可能，对一个剂量单位进一步提取，以确定在最初分析时是否提取完全。不完全提取可能使检验结果无效，也可导致检验方法无效的问题。

It is important that each step in the investigation be fully documented. Laboratory management should ascertain not only the reliability of the individual value obtained, but also the significance these OOS results represent to the laboratory quality assurance program. Laboratory management should be especially alert to developing trends. As part of an effective quality system, a firm's upper management should appropriately monitor these trends and ensure that any problematic areas are addressed. 调查的每一步都全部存档非常重要。实验室主管应确定，不仅个别数值的可靠性，这些OOS结果也代表了对实验室质量保证的程序的重大意义。实验室主管应特别注意发展趋势。作为有效质量体系的一部分，一个公司的上层管理应适当的监控这些趋势，并确保提出有问题的地方。

Laboratory error should be relatively rare. Frequent errors suggest a problem that might be due to inadequate training of analysts, poorly maintained or improperly calibrated equipment, or careless work. Whenever

laboratory error is identified, the firm should determine the source of that error and take corrective action to prevent recurrence. To ensure full compliance with the CGMP regulations, the manufacturer also should maintain adequate documentation of the corrective action. 实验室错误相对来说不应太多，频繁的错误暗示一个问题，那就是检验员培训不充分，设备维护保养不善或没有得到正确校正，或工作粗心。只要确定是实验室错误，公司应确定错误的来源，并采取改正措施以防再次发生。为了确保完全符合CGMP，制造商应持有改正措施的足够的文件。

In summary, when clear evidence of laboratory error exists, laboratory testing results should be invalidated. When evidence of laboratory error remains unclear, a full-scale OOS investigation should be conducted by the manufacturing firm to determine what caused the unexpected results. It should not be assumed that OOS test results are attributable to analytical error without performing and documenting an investigation. Both the initial laboratory assessment and the following OOS investigation should be documented fully. 总之，当有实验室错误的确切证据时，实验室检验结果应是无效的。当实验室错误的证据不够确切时，应有生产公司进行全面的OOS调查，以确定是什么引起了意外的结果。在没有进行调查和存档的情况下，不应假定OOS检验结果是由于分析错误。最初的实验室评估和以下的OOS调查都应全部存档。

## IV. INVESTIGATING OOS TEST RESULTS 对OOS结果的调查— PHASE II: FULL-SCALE OOS INVESTIGATION 第二步：全面OOS调查

When the initial assessment does not determine that laboratory error caused the OOS result and testing results appear to be accurate, a full-scale OOS investigation using a predefined procedure should be conducted. This investigation may consist of a production process review and/or additional laboratory work. The objective of such an investigation should be to identify the root cause of the OOS result and take appropriate corrective and preventative action.[7] A full-scale investigation should include a review of production and sampling procedures, and will often include additional laboratory testing. Such investigations should be given the highest priority. Among the elements of this phase is evaluation of the impact of OOS result(s) on already distributed batches. 如果初步评估表明不是实验室错误引起的OOS结果，结果又不正确的话，就要按事先规定的程序进行全面的OOS调查。该调查可能包括生产工艺回顾和／或附加的实验室工作。调查的目的的应是确定引起OOS结果的根本原因并采取适当的改正和预防措施。一个全面的调查应包括对生产和取样程序的回顾，并且经常包括附加的实验室检验。这样的调查有最高的优先权。在这一阶段的内容中，是评估OOS结果对已销售批次的影响。

### A. Review of Production 生产情况审核

The investigation should be conducted by the QCU and should involve all other departments that could be implicated, including manufacturing, process development, maintenance, and engineering. In cases where manufacturing occurs off-site (i.e., performed by a contract manufacturer or at multiple manufacturing sites), all sites potentially involved should be included in the investigation. Other potential problems should be identified and investigated. 调查应由质量管理部门执行，应包括所有涉及的部门，包括生产，工艺发展，维护和工程。如果生产不在当地（也就是由签约生产商生产或在多个生产地生产）调查应包括所有可能的生产地

[7] Please note that § 211.192 requires a thorough investigation of any discrepancy, including documentation of conclusions and follow-up. Implicit in this requirement for investigation is the need to implement corrective and preventative actions. Corrective and preventive action is consistent with the FDA's requirements under 21 CFR part 820, subpart J, pertaining to medical devices, as well as the 2004 draft guidance entitled *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*, which, when finalized, will represent the Agency's current thinking on this topic. 请注意§ 211.192 要求所有不符都要有一个彻底的调查，包括结论和跟踪的记录文件。此要求对调查而言即是需要实施纠正与预防措施，这些纠正与预防措施与 FDA 在 21CFR 820 部分章节 J 中涉及到医疗器械的要求是一致的，同时 2004 年起草的指南，名为药品 CGMP 质量体系方法，最终定稿时将代表当局在此问题上当前的想法。

点。其它可能的问题应确定和调查。生产工艺的记录和文件应全部再检查一遍，以确定引起OOS结果的可能原因。

The records and documentation of the manufacturing process should be fully reviewed to determine the possible cause of the OOS result(s). 应对生产记录和文件做全面的审核以确认可能的OOS原因。

A full-scale OOS investigation should consist of a timely, thorough, and well-documented review. A written record of the review should include the following information. 一个全面的OOS调查应包括及时的、彻底的及记录完整的审核。审核的书面记录应包括下述信息：

1. A clear statement of the reason for the investigation. 明确说明调查的原因。

2. A summary of the aspects of the manufacturing process that may have caused the problem. 对可能导致问题产生的生产工艺的各方面的总结。

3. The results of a documentation review, with the assignment of actual or probable cause. 对文件和审核结果，包括对实际原因和可能原因的归结。

4. The results of a review made to determine if the problem has occurred previously. 回顾以前生产中是否曾发生相同问题的结果。

5. A description of corrective actions taken. 采取的整改措施。

If this part of the OOS investigation confirms the OOS result and is successful in identifying its root cause, the OOS investigation may be terminated and the product rejected. However, a failure investigation that extends to other batches or products that may have been associated with the specific failure must be completed ( § 211.192). If any material was reprocessed after additional testing, the investigation should include comments and the signatures of appropriate production and quality control personnel. 如果在本部分OOS调查中，OOS结果被确认，且根本原因已被鉴别出，则OOS调查到此结束，该批次产品应被判定不合格。但是，扩展到别的批或产品不合格调查必须继续完成，别的批或产品可能与该结果有关(§ 211.192)。如果有物料在附加检验之后再经过加工，调查应包括适当的生产与质量控制人员的评论与签名。

OOS results may indicate a flaw in product or process design. For example, a lack of robustness in product formulation, inadequate raw material characterization or control, substantial variation introduced by one or more unit operations of the manufacturing process, or a combination of these factors can be the cause of inconsistent product quality. In such cases, it is essential that redesign of the product or process be undertaken to ensure reproducible product quality.[8] OOS结果可能预示了产品或工艺设计的缺点。比如，产品浓度不够，原材料鉴定和控制不够，生产工艺中一个或多个操作单元引入过多的变量，或这些因素的结合，这些都可能是产品质量不稳定的原因。在这些情况下，有必要重新设计产品或工艺以确保产品质量。

**B. Additional Laboratory Testing 附加化验室测试**

A full-scale OOS investigation may include additional laboratory testing. A number of practices are used during the laboratory phase of an investigation. These include (1) retesting a portion of the original sample and (2)

[8] OOS results might also be the result of the objectionable practice of making unauthorized or unvalidated changes to the manufacturing process.

resampling. 一个全面的OOS调查可能包括附加的实验室检验。在调查的实验室阶段，要用到很多规范。这些包括（１）对一部分原样复验和（２）重新取样。

*1. Retesting 复测*

Part of the investigation may involve *retesting* of a portion of the original sample. The sample used for the retesting should be taken from the same homogeneous material that was originally collected from the lot, tested, and yielded the OOS results. For a liquid, it may be from the original unit liquid product or composite of the liquid product; for a solid, it may be an additional weighing from the same sample composite prepared for the original test. 部分调查可能包括一部分原样的复验。用于复验的样品应该是最初收集检验的、出现OOS结果的样品均质物料的一部分。如果是液体，可以是液体成品的原始单位或液体成品的混合物。如果是固体，可以是分析员制备的相同混合物的额外的称量。

Situations where retesting is indicated include investigating testing instrument malfunctions or to identify a possible sample handling problem, for example, a suspected dilution error. Decisions to retest should be based on the objectives of the testing and sound scientific judgment. It is often important for the predefined retesting plan to include retests performed by an analyst other than the one who performed the original test. A second analyst performing a retest should be at least as experienced and qualified in the method as the original analyst. 原样复验旨在调查检测设备故障或确定样品处理上可能存在的问题，例如可疑的稀释错误等。决定复验应依据检验的客观和合理的科学判断。复验计划非常重要的一点是原样复验必须由另一名分析员执行，而不是原先的分析员执行。第二个分析员至少和第一个分析员一样有经验和有资格。

The CGMP regulations require the establishment of specifications, standards, sampling plans, test procedures, and other laboratory control mechanisms (§ 211.160). CGMP要求建立规范，标准，取样计划，检验程序和其它实验室控制体制(§ 211.160)。

FDA inspections have revealed that some firms use a strategy of repeated testing until a passing result is obtained, then disregarding the OOS results without scientific justification. This practice of “testing into compliance” is unscientific and objectionable under CGMPs. The maximum number of retests to be performed on a sample should be specified in advance in a written standard operating procedure (SOP). The number may vary depending upon the variability of the particular test method employed, but should be based on scientifically sound principles. The number of retests should not be adjusted depending on the results obtained. The firm's predetermined retesting procedures should contain a point at which the additional testing ends and the batch is evaluated. If the results are unsatisfactory at this point, the batch is suspect and must be rejected or held pending further investigation (§ 211.165(f)). Any deviation from this SOP should be rare and done in accordance with § 211.160(a), which states that any deviations from written specifications, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified. In such cases, before starting additional retesting, a protocol should be prepared (subject to approval by the QCU) that describes the additional testing to be performed and specifies the scientific and/or technical handling of the data. FDA检查显示，有些公司重复检验直到得到满意的结果，然后剔除没有科学依据的OOS结果。按照CGMPs检验至合格是不科学和不充许的。一个样品复验的最多次数应事先在SOP明确规定。不同的检验方法允许复验的次数可能不同，但应遵守科学合理原则。复验次数不能根据结果调整。公司的预先确定的复验程序应包括一个点，在这个点检验终止和进行批评估。如果在这个点结果不满意，则怀疑批，批不合格或待进一步调查(§ 211.165(f))。按照§ 211.160(a)不应背离SOP，§ 211.160(a)规定，任何背离书

面规定，取样计划，检验程序或其它实验室控制制度应予记录和证明是正当的。在这种情况下，在复验前，应准备规程（由质量管理部门批准）描述附加的检验并明确提出数据的科学和／或技术的处理。

In the case of a clearly identified laboratory error, the retest results would substitute for the original test result. All original data should be retained, however, and an explanation recorded. This record should be initialed and dated by the involved persons and include a discussion of the error and supervisory comments. (See section III of this guidance for more details on a laboratory investigation.) 在明确确定了实验室错误的情况下，原样复验结果合格，再检验结果将取代最初检验结果。应保留所有原始数据，但也应有解释性的记录。应该保留最初结果注明测定结果无效，在OOS调查记录上应有相关人员的签名、日期的标明，并应包括对错误的讨论和主管的注释。(详见本指南第三部分III实验室调查)

If no laboratory or calculation errors are identified in the first test, there is no scientific basis for invalidating initial OOS results in favor of passing retest results. All test results, both passing and suspect, should be reported [9] and considered in batch release decisions. 首次检验时若没有实验室错误或统计错误发生，就没有科学基础使原来的OOS结果无效，使复验结果通过。所有的检验结果，通过的和可疑的，都应有报告，在批放行中考虑。

*2. Resampling 重新取样*

While retesting refers to analysis of the original, homogenous sample material, *resampling* involves analyzing a specimen from any additional units collected as part of the original sampling procedure or from a new sample collected from the batch, should that be necessary. 重新取样指对已出现不合格结果的样品，按规定的取样规程，从同一批号样品中重新另取的第二组样品，供另外增加化验使用。目的是调查样品可能存在的问题。

The original sample from a batch should be sufficiently large to accommodate additional testing in the event an OOS result is obtained. In some situations, however, it may be appropriate to collect a new sample from the batch. Control mechanisms for examination of additional specimens should be in accordance with predetermined procedures and sampling strategies (§ 211.165(c)). 同一批的原始的样品应有足够的量，万一出现OOS结果时以供附加的检验。但有的情况下，也可以从同一批中收集新的样品。附加样的检验控制应按照原先确定的程序和取样方法(§ 211.165(c)。

When all data have been evaluated, an investigation might conclude that the original sample was prepared improperly and was therefore not representative of the batch quality (§ 211.160(b)(3)). Improper sample preparation might be indicated, for example, by widely varied results obtained from several aliquots of an original composite (after determining there was no error in the performance of the analysis). Resampling should be performed by the same qualified, validated methods that were used for the initial sample. However, if the investigation determines that the initial sampling method was inherently inadequate, a new accurate sampling method must be developed, documented, and reviewed and approved by the QCU (§§ 211.160 and 211.165(c)). 对所有的数据评估，调查的结论可能是原来

[9] In other words, all data are reported in, for example, quality control reports, batch records, Certificates of Analysis, in accordance with §§ 211.188 and 211.192. 换而言之，所有数据报告，如质量检测报告，批报告，分析报告应符合211章188和211章192的要求。

的样品配制不当，所以不具有批质量的代表性(§ 211.160(b)(3)。这可由多种情形判定，如对原样不同部分进行检测，结果大范围波动（确定分析操作没有错误后）。重新取样应按照检测原样所使用的取样方法进行。若调查确定了原来的取样方法不正确，则须开发一个新的正确方法，并由QCU批准颁布实施。(§§ 211.160和211.165(c))

**C. Reporting Testing Results 报告测试结果**

Practices used in reporting and interpretation of test results include (1) averaging and (2) outlier tests. 对检验结果的报告和解释包括取平均值和异常结果检测。

*1. Averaging 平均值*

There are both appropriate and inappropriate uses of averaging test data during original testing and during an OOS investigation: 在原始检测和OOS调查中，平均值可能会被正确使用，也可能会被误用。

a. Appropriate uses 正确使用

Averaging data can be a valid approach, but its use depends upon the sample and its purpose. For example, in an optical rotation test, several discrete measurements are averaged to determine the optical rotation for a sample, and this average is reported as the test result. If the sample can be assumed to be homogeneous, (i.e., an individual sample preparation designed to be homogenous), using averages can provide a more accurate result. In the case of microbiological assays, the U.S. Pharmacopeia (USP) prefers the use of averages because of the innate variability of the biological test system. 取平均值可能是一个好的方法，但这取决于样品及其目的。例如，在比旋的检测中，几次独立检测得到的数据被取平均值作为一个样品的比旋。如果该样品被假定是均一的，（也就是说一个独立制备的样品假定是均一的）取平均值可以提供一个更准确的结果。在微生物含量测试中，美国药典倾向于取取平均值，因为生物检测系统本身具有不稳定性。

It should be noted that a test might consist of a specific number of replicates to arrive at a result. For instance, an HPLC assay result may be determined by averaging the peak responses from a number of consecutive, replicate injections from the same preparation (usually 2 or 3). The assay result would be calculated using the peak response average. This determination is considered one test and one result. This is a distinct difference from the analysis of different portions from a lot, intended to determine variability within the lot, and from multiple full analyses of the same homogenous sample. The use of replicates to arrive at a single reportable[10] result, and the specific number of replicates used, should be specified in the written, approved test method. Acceptance limits for variability among the replicates should also be specified in the method. Unexpected variation in replicate determinations should trigger remedial action as required by § 211.160(b)(4). If acceptance limits for replicate variability are not met, the test results should not be used. 这里应该注意的是，一次检验可能由一定的平行测定得到一个结果。比如，HPLC检验结果是由同一溶液的一组连续的，平行的进样的峰值平均得来的（通常是2或3）。这种测定是一次检验一个结果。这与一批中不同部分的分析明显不同，也与同一均质样品的多元全面分析不同。平行测定以得到最终结果，和平行测定的次数，应在书面的经批准的检验

[10] The term *reportable result* as used in this document means a final analytical result. This result is appropriately defined in the written approved test method and derived from one full execution of that method, starting from the original sample.术语“可报告的结果”当用于本文中时，表示一个最终分析结果。该结果应是对一个原始样品，严格按照书面批准的检验方法进行完整的检验并计算所得的结果。

方法中明确规定。平行测定中变化范围也应在方法中明确规定。按§ 211.160(b)(4)要求，平行测定中意料外的变化要采取矫正措施。如果不符合平行测定范围，检验结果不能用。

In some cases, a *series* of complete tests (full run-throughs of the test procedure), such as assays, are part of the test method. It may be appropriate to specify in the test method that the average of these multiple assays is considered one test and represents one reportable result. In this case, limits on acceptable variability among the individual assay results should be based on the known variability of the method and should also be specified in the test methodology. A set of assay results not meeting these limits should not be used. 有时，检验方法可能包括若干完整的单个检验项目，如含量。此时应该在检验方法中明确说明数次检验结果的平均值作为一个检验结果报告。这时，各结果之间的允许的变动性应在方法中明确表述。如果一系列结果达不到该要求则不应取用。

These appropriate uses of averaging test data should be used during an OOS investigation only if they were used during the original testing that produced the OOS result. 仅仅当在产生OOS结果的原始检验中使用此平均值时，该平均值才会在OOS调查中被采用。

b. Inappropriate uses 不正确使用

Reliance on averaging has the disadvantage of hiding variability among individual test results. For this reason, all individual test results should normally be reported as separate values. Where averaging of separate tests is appropriately specified by the test method, a single averaged result can be reported as the final test result. In some cases, a statistical treatment of the variability of results is reported. For example, in a test for dosage form content uniformity, the standard deviation (or relative standard deviation) is reported with the individual unit dose test results. 用平均法有掩蔽单个数据差异的弊端。由于这个原因，所有单个数据差异通常应单独报告。在检验方法中明确适用平均法的，平均结果可以做为检验结果。在一些情况下，报告变异结果的统计学处理。例如，在剂型含量均匀度的检验中，报告标准偏差（相对偏差）和单个剂型的检验结果。

Averaging can also conceal variations in different portions of a batch, or within a sample. For example, the use of averages is inappropriate when performing powder blend/mixture uniformity or dosage form content uniformity determinations. In these cases, testing is intended to measure variability within the product, and individual results provide the information for such an evaluation. 平均值可能会掩盖同一批中或同一样品中质量的不均一性。例如，当检验粉末混合均一性，或制剂含量均一性性时对数据进行平均是不合适的。在这种情况下，检测的目的就是要测试产品的均匀性质，单个的检测结果才可以为这样的评价提供信息。

In the context of additional testing performed during an OOS investigation, averaging the result(s) of the original test that prompted the investigation and additional retest or resample results obtained during the OOS investigation is not appropriate because it hides variability among the individual results. Relying on averages of such data can be particularly misleading when some of the results are OOS and others are within specifications. It is critical that the laboratory provide all individual results for evaluation and consideration by the QCU, which is responsible for approving or rejecting, e.g., drug products, in-process materials (§ 211.22) 在OOS调查的附加检验中，平均最初检验的结果，加快调查和复验或得到重新取样的结果，是不适当的，因为它掩蔽了各个结果之间的差异。当出现一些是OOS结果而其它结果的符合规定时，这些数据的平均尤其会造成误解。实验室提供所有单个结果非常重要，这些结果用于QCU评估和考虑，QCU负责批准或否定，如药品，在制品(§ 211.22)。

For example, in an assay of a finished drug with a specification of 90 to 110 percent, an initial OOS result of 89 percent followed by additional retest results of 90 percent and 91 percent would produce an average of 90 percent. While this average would meet specifications,[11] the additional test results also tend to confirm the original OOS result. However, in another situation with the same specifications, an initial OOS result of 80 percent followed by additional test results of 85 percent and 105 percent would also produce an average of 90 percent, but present a much different picture. These results do not confirm the original OOS result but show high variability and may not be reliable. In both examples, the individual results, not the average, should be used to evaluate the quality of the product. 例如，某制剂的含量标准为90-110%，初始OOS结果为89%，接着增加的复测结果为90%，91%，它们三者的平均值为90%。虽然这个平均值符合质量标准，附加测试结果亦倾向于肯定初始的OOS结果，但如果在相同的质量标准情况下，初始OOS结果为80%，附加测试结果为85%和105%，同样会得到90%的平均值，而这时呈现出完全不同的现象。这些结果并不能肯定初始OOS结果，而显示出高度的分散性，可能并不可靠。在上述两个例子中，应采用单独的结果，而不是平均值对产品的质量进行评价。

*2. Outlier Tests 异常值（离群值）检验*

The CGMP regulations require that statistically valid quality control criteria include appropriate acceptance and/or rejection levels (§ 211.165(d)). On rare occasions, a value may be obtained that is markedly different from the others in a series obtained using a validated method. Such a value may qualify as a statistical outlier. An outlier may result from a deviation from prescribed test methods, or it may be the result of variability in the sample. It should never be assumed that the reason for an outlier is error in the testing procedure, rather than inherent variability in the sample being tested. CGMP(§ 211.165(d))要求统计上有效的质量控制标准应包括适当的接受和否定标准。在极少情况下，使用验证过的的方法也会得到一个与其他值明显不同的数值。该值被视为统计上的逸出值。一个逸出值可由既定检验方法的偏差中产生或是样品波动的一个结果。不应认为逸出理由是检验错误而不是待测样品检验时固有的波动。

Outlier testing is a statistical procedure for identifying from an array those data that are extreme. The possible use of outlier tests should be determined in advance. This should be written into SOPs for data interpretation and be well documented. The SOPs should include the specific outlier test to be applied with relevant parameters specified in advance. The SOPs should specify the minimum number of results required to obtain a statistically significant assessment from the specified outlier test. 异常值检验是一个统计程序，用以将一些离群数值从一组数据中鉴别出来。对异常值检验程序的使用应提前决定，并在数据诠释的SOP中写明并以文件形式记录。SOP应包括将采用的详细的异常值检验方法，并事先指定相关的参数。SOP应规定为得到统计学显著性评估结论，进行异常值检验所需要的最少数据量。

For biological assays having a high variability, an outlier test may be an appropriate statistical analysis to identify those results that are statistically extreme observations. The USP describes outlier tests in the general chapter on *Design and Analysis of Biological Assays* <111>.[12] In these cases, the outlier

[11] When arriving at a batch disposition decision, it is important for a firm to assess whether the low assay value may project to a subpotency failure before the product's labeled expiration date.在对一个批次产品作出处理决定前，有一点很重要是公司在对有效期进行标准前应评价低的含量是否会导致产品在效期内因含量降低而不合格。

[12] *The United States Pharmacopeia*, 29th Revision, Rockville, MD: The United States Pharmacopeial Convention, 2006. 美国药典，29 版，美国药典委员会，2006。

observation is omitted from calculations. The USP also states that "arbitrary rejection *or* retention of an apparently aberrant response can be a serious source of bias… the rejection of observations solely on the basis of their relative magnitudes is a procedure to be used sparingly" (USP <111>).由于生物含量测定有很高的可变性，确定那些是极端值的结果时，用逸出值检验可能是适当的统计学分析。USP在Design and Analysis of Biological Assays <111>中描述了逸出值检验。在这此情况下，计算时可以忽略逸出值。USP也规定"武断的否定或保留一个明显的异常值是偏差的来源单独依据它们的相对重要性否定异常值很少使用"(USP<111>)。

For validated chemical tests with relatively small variance, and if the sample being tested can be considered homogeneous (for example, an assay of a composite of a dosage form drug to determine strength), an outlier test is only a statistical analysis of the data obtained from testing and retesting. It will not identify the cause of an extreme observation and, therefore, should not be used to invalidate the suspect result. Occasionally, an outlier test may be of some value in estimating the probability that the OOS result is discordant from a data set, and this information can be used in an auxiliary fashion, along with all other data from the investigation, to evaluate the significance of the result. 对于有效的，相对很少变化的化学检验，如果待测样品可以认为是均匀的（如化验剂量单位合成物的含量的浓度），逸出值检验仅仅是对检验和复验中得数据的统计分析。没有确定极值的原因，因此，不应该用来确定怀疑值无效。偶尔，一个逸出值检验在估计OOS结果与一批数据不一致的可能性时有用，这些信息可以以一种辅助的形式和其它调查数据一起使用，来估价结果的显著性。

Outlier tests have no applicability in cases where the variability in the product is what is being assessed, such as for content uniformity, dissolution, or release rate determinations. In these applications, a value perceived to be an outlier may in fact be an accurate result of a nonuniform product. 在产品评估中含有可变性的情况下，不应用逸出值检验，如含量均匀度，溶解或释放速率的测定。在这样的应用中，一个逸出值事实上可能是不均匀产品的准确结果。

When using these practices during the additional testing performed in an OOS investigation, the laboratory will obtain multiple results. It is again critical for the laboratory to provide all test results for evaluation and consideration by the QCU in its final disposition decision. In addition, when investigation by a contract laboratory[13] does not determine an assignable cause, all test results should be reported to the customer on the certificate of analysis. 在OOS调查的附加检验中使用这些惯例，实验室将得到多种结果。实验室提供所有检验结果供QCU最终处理中评估和考虑非常重要。另外，如果签约实验室进行的调查没有确定原因，所有的检验结果都应在检验报告中报告给客户。

## V. CONCLUDING THE INVESTIGATION 调查结论

To conclude the investigation, the results should be evaluated, the batch quality should be determined, and a release decision should be made by the QCU. The SOPs should be followed in arriving at this point. Once a batch has been rejected, there is no limit to further testing to determine the cause of the failure so that a corrective action can be taken. 要对调查作出结论的话，应对所有结果进行评价，对涉及的批次质量进行确认，质量部门对产品作出放行结论。以上行为应根据相关SOP进行。一旦一个批次被判定不合格，为了找出不合格的原因，对于此批次的检测不再受到任何限制，以便制定相应的整改措施。

[13] The Agency also recommends that OOS investigation reports be provided to the customer.代理亦会建议将 OOS 调查报告提交给客户。

**A. Interpretation of Investigation Results 调查结果解释**

The QCU is responsible for interpreting the results of the investigation. An initial OOS result does not necessarily mean the subject batch fails and must be rejected. The OOS result should be investigated, and the findings of the investigation, including retest results, should be interpreted to evaluate the batch and reach a decision regarding release or rejection (§ 211.165). 质量部门应负责对调查的结果进行解释。初步的OOS结果并不表示该批次一定是不合格不可以放行的。对OOS结果需要进行调查，调查中的发现，包括复试结果应加以解释以对该批次作出评价，并从中得出放行或不放行的结论。

In those instances where an investigation has revealed a cause, and the suspect result is invalidated, the result should not be used to evaluate the quality of the batch or lot. Invalidation of a discrete test result may be done only upon the observation and documentation of a test event that can reasonably be determined to have caused the OOS result. 如果调查发现了OOS的原因，并认为可疑数据是无效结果，那么该检验数据不应用于该批次的质量评价。只有在观察到的现象与文件记录表明会导致OOS结果时，才可判定一个与其它数据趋势不符的数据为无效数据。

In those cases where the investigation indicates an OOS result is caused by a factor affecting the batch quality (i.e., an OOS result is confirmed), the result should be used in evaluating the quality of the batch or lot. A confirmed OOS result indicates that the batch does not meet established standards or specifications and should result in the batch's rejection, in accordance with § 211.165(f), and proper disposition. For inconclusive investigations — in cases where an investigation (1) does not reveal a cause for the OOS test result and (2) does not confirm the OOS result — the OOS result should be given full consideration in the batch or lot disposition decision. 如果调查显示OOS结果是由影响批质量的一个因素引起的（也就是说OOS结果被证实了），则结果应该用来评估本批或更多批的质量。按照§ 211.165(f)一个经确证后的OOS结果表明这批质量不符合已确定标准或规格，结果应为不合格并进行恰当的处理。对未得出结论的调查—（1）没有找出OOS的原因和（2）没有证实OOS结果—OOS结果在批处理更多批决定中应予充分考虑。

In the first case (OOS confirmed), the investigation changes from an OOS investigation into a batch failure investigation, which must be extended to other batches or products that may have been associated with the specific failure (§ 211.192). 在第一种情况下（OOS结果被肯定），则偏差调查从一个OOS调查变成一个不合格批的调查，此时，调查必须延伸至其他与该不合格因素相关的批次或产品（211章192部分）。

In the second case (inconclusive), the QCU might still ultimately decide to release the batch. For example, a firm might consider release of the product under the following scenario: 在第二种情况下（不能确认），QCU可能最终还是会决定将该批放行。例如，公司可能会在下列设想下考虑放行产品

A product has an acceptable composite assay range of 90.0 to 110.0 percent. The initial (OOS) assay result is 89.5 percent. Subsequent sample preparations from the original sample yield the following retest results: 99.0, 98.9, 99.0, 99.1, 98.8, 99.1, and 99.0 percent. A comprehensive laboratory investigation (Phase 1) fails to reveal any laboratory error. Review of events during production of the batch reveals no aberrations or indication of unusual process variation.[14] Review of the manufacturing process and product history demonstrates that the process is robust. The seven passing retest results are all well within the known limits of variability of the method used. Batch results from in-process monitoring, content uniformity, dissolution, and other tests are consistent with the passing retest results. After a thorough investigation, a firm's QCU might conclude that the

[14] As an example, evaluation of process variation would determine if established equipment, facility, and process control limits were met. 工艺波动例子，如设备、公用系统或工艺控制的实际值达到设定的限度。

initial OOS result did not reflect the true quality of the batch. 一个产品的含量有一个可接受范围90.0-110.0%. 首次报告OOS含量结果为89.5%，初始样在重新制样后得到下列复试结果：99.0%, 98.9%, 99.0%, 99.1%, 98.8%, 99.1%, 99.0%。化验室综合调查（第一阶段）并未发现化验室错误。对该批生产过程的审核未发现异常或生产工艺波动。该批生产的审核及该产品的历史回成表明工艺是稳定的。7个复测结果之间的误差在方法可以接受的范围之内。批分析结果从中间控制、产品均一性、产品分散性和其他检测均与复测结果相吻合。经过彻底调查后，公司的质量部门可能认为首次报告的OOS结果不能真实反映该批产品的质量。

It is noteworthy in this scenario that the original, thorough laboratory investigation failed to find any assignable cause. However, if subsequent investigation nonetheless concludes that the source of the OOS result was a cause unrelated to the manufacturing process, in response to this atypical failure to detect the laboratory deviation, it is essential that the investigation include appropriate follow-up and scrutiny to prevent recurrence of the laboratory error(s) that could have led to the OOS result. 值得注意的是此假想有一个前提，即在初始的完整化验室调查中，并未发现任何可归结原因。尽管如此，如果接下来的调查得出结论OOS结果并非由生产工艺因素引起，对于这样反映出化验室偏差的非典型失误，化验室应采取相应的跟踪措施或详细审查，以避免相同的化验室错误导致OOS结果。

As the above example illustrates, any decision to release a batch, in spite of an initial OOS result that has not been invalidated, should come only after a full investigation has shown that the OOS result does not reflect the quality of the batch. In making such a decision, the QCU should always err on the side of caution. 在上述例子中，在做出任何放行该批的决定时，即使首次报告的OOS结果并未确认无效，应该进行彻底的调查以证明该OOS结果未能反映该批产品的质量。在做出这样的决定时，质量部门应倾向于更谨慎的选择。

**B. Cautions 注意事项**

In cases where a series of assay results (to produce a single reportable result) are required by the test procedure and some of the individual results are OOS, some are within specification, and all are within the known variability of the method, the passing results are no more likely to represent the true value for the sample than the OOS results. For this reason, a firm should err on the side of caution and treat the reportable average of these values as an OOS result, even if that average is within specification. This approach is consistent with the principle outlined in the USP General Notices that an official article shall comply with the compendial standard any time a compendial test is applied.[15] Thus, every individual application of the official test should be expected to produce a result that meets specifications. 如果检验程序要求得到一组含量结果（以产生一个单一的报告结果），而这一组含量结果中部分结果是OOS，部分结果符合质量标准，并且所有的结果均在已知的方法误差范围内，好的结果并不比OOS结果更能代表样品的真实值。由于该原因，公司应该倾向于更谨慎，将这些检测值的平均值报告为OOS结果，即使平均值仍符合质量标准。这种方法与USP通则中概述的原则相一致，这样，每一个官方单独检测均可以得到符合质量标准的结果。

An assay result that is low, but within specifications, should also raise a concern. One cause of the result could be that the batch was not formulated properly. Batches must be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient (§ 211.101 (a)). This would also be a situation where the analytical result meets specifications, but caution should be used in the release or reject decision. 如果含量结果较低，但仍在合格范围内，应引起重视。这种结果的原因之一可能是该批配方不适当。一批产品的配方应是能提供不低于标示含量或活性成份数量的100%（§ 211.101 (a)）。这种情况下，

[15] See USP 29, *General Notices*, "Test Results, Statistics, and Standards."见美国药典 29，凡例，"检验结果、统计和标准"。

检测结果仍是符合规定的，但在作出放行或不放行决定时应谨慎。

As with all analytical testing conducted to evaluate the quality of a drug, all records pertaining to the OOS test result should be retained. Records must be kept of complete data derived from all tests performed to ensure compliance with established specifications and standards (§ 211.194). 尽管检测是用来评价一种药品的质量，所有与OOS检测结果相关的记录均应封存。记录必须包括所有检验的完整数据以保证与已有质量标准相符合。

**C. Field Alert Reports**

For those products that are the subject of approved full and abbreviated new drug applications, regulations require submitting within 3 working days a field alert report (FAR) of information concerning any failure of a distributed batch to meet any of the specifications established in an application (21 CFR 314.81(b)(1)(ii)). OOS test results on these products are considered to be one kind of "information concerning any failure" described in this regulation. Unless the OOS result on the distributed batch is found to be invalid within 3 days, an initial FAR should be submitted. A follow-up FAR should be submitted when the OOS investigation is completed.对于已批准的ANDA或NDA产品，法规要求在三个工作日内提交现场警示报告（FAR），报告已销售批次的任何不符合申请文件（21 CFR 314.81(b)(1)(ii)）中的质量标准的情况。这些产品的OOS检验结果被认为是法规所描述的“任何相关失败信息”的一种。除非已销售批次的OOS结果在三个工作日内被确认为无效，否则应提交初始FAR。当OOS调查结束时，应提交FAR跟踪报告。