Geometry proofs practice worksheets with answers

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Advertisement Advertisement Advertisement Calculating simple interest is an essential skill for anyone who maintains a bank account, carries a credit card balance, or applies for a loan. The free printable worksheets in this lesson will improve your homeschool math lessons and help your students become better at calculations. This collection of worksheets will also help students understand the process using word problems. Answers are provided for each of the five worksheets on the second page for ease of grading. Before having students start on the worksheets, explain that when you borrow money, you have to repay the amount you borrowed as well as any added interest charges, which represents the cost of borrowing. In the same way, explain to students that when you lend money or deposit funds in interest-bearing accounts, you typically earn interest income for making your money available to other people. D. Russell Print the PDF: Simple Interest Worksheet No. 1 In this exercise, students will answer 10 word problems about calculating interest. These exercises will help homeschoolers learn how to calculate the rate of return on investments and illustrate how interest can accrue over time. Students will answer such questions as, "How much interest does a $318 investment earn at 9 percent over one year?" Explain to students that the answer would be $28.62 because $318 x 9 percent is the same as $318 x 0.09, which equals $28.62. Explain to students that they would have to pay this amount of interest in addition to repaying the principal, the amount of the original loan, $318. D. Russell Print the PDF: Simple Interest Worksheet No. 2 These 10 questions will reinforce the lessons from worksheet No. 1. Homeschoolers and other students will learn how to calculate rates and determine interest payments. For this PDF, students will answer word problem questions such as: "If the balance at the end of eight years on an investment of $630 that has been invested at a rate of 9 percent is $1,083.60, how much was the interest?" If students are struggling, explain that calculating this answer involves only simple subtraction, where you subtract the initial investment of $630 from the ending balance of $1,083.60. Students would set up the problem as follows: $1,083.60 – $630 = $453.60 Explain that some of the information in the question was extraneous and not necessary to solve the problem. For this problem, you don't need to know the years of the loan (eight years) or even the interest rate; you only need to know the beginning and ending balance. D. Russell Print the PDF: Simple Interest Worksheet No. 3 Use these word questions to continue practicing how to calculate simple interest. Students can also use this exercise to learn about the principal, rate of return (the net gain or loss on an investment over a specified time), and other terms commonly used in finance. D. Russell Print the PDF: Simple Interest Worksheet No. 4 Teach your students the basics of investing and how to determine which investments will pay the most over time. This worksheet will help your homeschoolers polish their calculating skills. D. Russell Print the PDF: Simple Interest Worksheet No. 5 Use this final worksheet to review the steps for calculating simple interest. Take time to answer questions your homeschoolers may have about how banks and investors use interest calculations. As much as a franchise might help ease you into business, choosing which one to buy is a major decision that will shape the course of your life. For those of you who want to buy a franchise but aren't quite sure where to start, look no further--we went out and did the legwork for you. We asked franchisees, franchisors and experts what they consider to be the top questions across all categories, including money and financing, personal satisfaction with the franchise, finding a business with the right fit, and system issues. To help you on your journey, we've compiled a list of the top 10 questions to ask yourself, franchisors and existing franchisees.And just to give you one more helpful nudge, we even got the inside scoop on how to interpret the answers you receive. So fire away. After all, it's your due diligence from this point on that will really determine your future success. Many leading analytical balance manufacturers provide built-in "auto-calibration" features in their balances. Are such auto-calibration procedures acceptable instead of external performance checks? If not, then what should the schedule for calibration be? Does CGMPs require that forced degradation studies always be conducted of the drug product when determining if a drug product stability test method is stability indicating? When performing the USP General Chapter Particulate Matter in Injections test for a large volume parenteral (LVP), is it acceptable to take the average among the units tested to determine if the batch meets its specification for this attribute? Can Total Organic Carbon (TOC) be an acceptable method for detecting residues of contaminants in evaluating cleaning effectiveness? Would a paramagnetic or laser oxygen analyzer be able to detect all possible contaminants or impurities in a medical gas? Can up to 12-month expiration dating be assigned to oral solid and liquid dosage forms repackaged into unit-dose containers based on guidance in the May 2005 draft revision of Compliance Policy Guide Sec. 480.200 Expiration Dating of Unit Dose Repackaged Drugs (CPG 7132b.11)? Is it ever appropriate to use an unvalidated method to test a drug component or product? Did FDA withdraw the 1987 Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices? Where can drug manufacturers find information regarding endotoxin testing? Is it acceptable to release non-penicillin finished drug products to market if the products may have been exposed to penicillin, as long as the non-penicillin products are tested and no penicillin residue is found? Can a facility that produced penicillin dosage forms be decontaminated and renovated for production of non-penicillin dosage forms, provided there is no further penicillin production in the renovated facility? Is there an acceptable level of penicillin residue in non-penicillin drug products? For injectable drugs in multiple-dose containers, is the number of entries to withdraw a dose a factor in determining the expiration date? How long may a firm store in-process/intermediate powder blends and triturations, sustained-release pellets/beads, and tablet cores, absent separate stability studies, before using them in finished drug products? What material can be used as instrument calibration standards for chromatographic systems? What material can be used for system suitability? Is it ever appropriate to perform a “trial injection” of samples? 1. Many leading analytical balance manufacturers provide built-in "auto calibration" features in their balances. Are such auto-calibration procedures acceptable instead of external performance checks? If not, then what should the schedule for calibration be? The auto-calibration feature of a balance may not be relied upon to the exclusion of an external performance check (21 CFR 211.68). For a scale with a built-in auto-calibrator, we recommend that external performance checks be performed on a periodic basis, but less frequently as compared to a scale without this feature. The frequency of performance checks depends on the frequency of use of the scale and the criticality and tolerance of the process or analytical step. Note that all batches of a product manufactured between two successive verifications would be affected should the check of the auto-calibrator reveal a problem. Additionally, the calibration of an auto-calibrator should be periodically verified—a common frequency is once a year—using National Institute of Standards and Technology (NIST)-traceable standards or NIST-accredited standards in use in other countries. References: 21 CFR 211.68: Automatic, mechanical, and electronic equipment 21 CFR 211.160(b)(4): General requirements (Laboratory Controls) United States Pharmacopeia (USP) General Chapter Weights and Balances See also ASTM standard E 617, 2013, Standard Specification for Laboratory Weights and Precision Mass Standards, West Conshohocken, PA: ASTM International (This standard is incorporated into the USP by reference; other widely recognized standards may be acceptable) Back to Top 2. Do CGMPs require that forced degradation studies always be conducted of the drug product when determining if a drug product stability test method is stability indicating? No. Drug product stress testing (forced degradation) may not be necessary when the routes of degradation and the suitability of the analytical procedures can be determined through use of the following: Data from stress testing of the drug substance Reference materials for process impurities and degradants Data from accelerated and long-term studies on the drug substance Data from accelerated and long-term studies on the drug product Additional supportive information on the specificity of the analytical methods and on degradation pathways of the drug substance may be available from literature sources. Section 211.165(e) of the CGMP regulations states that the accuracy, sensitivity, specificity, and reproducibility of test methods shall be established and documented (21 CFR 211.165(e)). Further, 21 CFR 211.166(a)(3) requires that stability test methods be reliable, meaningful, and specific, which means that the content of the active ingredient, degradation products, and other components of interest in a drug product can be accurately measured without interference, often called stability indicating. The CGMP regulations do not specify what techniques or tests are to be used to ensure that one’s test methods are stability indicating. However, evaluating the specificity of the test methods during forced degradation studies (i.e., exposing the drug to extremes of pH, temperature, oxygen, etc.) of the drug substance and drug product often is necessary to ensure that stability test methods are stability indicating. But in certain circumstances, conducting a forced degradation study of just the drug substance may be sufficient to evaluate the stability-indicating properties of a test method. Generally, in determining whether it is necessary to conduct forced degradation studies of the drug product, the specificity of the test method should be evaluated for its ability to assay drug substance, degradants, and impurities, in the presence of each other, without interference. The evaluation also should provide assurance that there is not a potential for interaction between the drug substance, degradants, impurities, excipients, and container-closure system during the course of the shelf life of the finished drug product. Last, the rationale for any decision made concerning the extent of the forced degradation studies conducted as well as the rationale for concluding that a test method is stability indicating should be fully documented. References: 21 CFR 211.137: Expiration dating 21 CFR 211.165(e): Testing and release for distribution 21 CFR 211.166(a)(3): Stability testing Compliance Policy Guide Sec. 480.100 Requirements for Expiration Dating and Stability Testing (CPG 7132a.04) Back to Top 3. When performing the USP General Chapter Particulate Matter in Injections test for a large volume parenteral (LVP), is it acceptable to take the average among the units tested to determine if the batch meets its specification for this attribute? No. It is not acceptable to take the average among the LVP units tested in each batch/lot when following this method because the purpose of this method is to measure and limit intra-batch variability. Particulate matter refers to small, subvisible particles. General Chapter provides two tests for detecting such particulates—light obscuration and microscopic assay. Both are generally accepted for use in testing LVPs and small volume parenterals (SVP) for the determination of subvisible particulate matter. Normally, samples are first tested by the light obscuration method; if the sample fails the specified limits, the microscopic assay method can then be used. However, the microscopic method can be the sole test if there is a documented technical reason or interference from the product under test that would make the light obscuration method unsuitable or the results invalid. Confusion about when averaging data is and is not acceptable is probably due to the sample preparation method for the light obscuration test (General Chapter). At least 2, 5-mL aliquots from each sampled unit or the pooled sample (see below) are to be used in the particulate count determination, and the results from these aliquots are to be averaged for comparison with the specification. Note that the average is of the results from examining each aliquot and not between units. (The results of the first aliquot examined by light obscuration are to be discarded, and the subsequent aliquots—2 or more—are retained.) Pooling units prior to analysis is permitted only if the volume in each unit is less than 25 mL, in which case 10 or more units may be pooled. If the volume in the SVP or LVP is 25 mL or more per unit, single units are to be examined by this method (General Chapter). Results among the test units cannot be averaged because particulate matter is assumed to be non-uniformly dispersed throughout the lot. The intent of assessing results from each individual unit is to ensure adequate representation of the lot and to detect potential variation within a lot. As to the number of individual units to be tested for LVP and SVP units having a volume of 25mL or more, the USP states that the number of units tested depends on "statistically sound sampling plans," and "sampling plans should be based on consideration of product volume, numbers of particles historically found to be present in comparison to limits, particle size distribution of particles present, and variability of particle counts between units." The USP also suggests that the total number of units tested for any given batch may be less than 10 units (for LVP and pooled SVPs) with proper justification. This is consistent with the CGMP requirement for statistical sampling plans (see 21 CFR 211.165). References: 21 CFR 211.160: General requirements (Laboratory Controls) 21 CFR 211.165(c)(d): Testing and release for distribution USP General Chapter Particulate Matter in Injections FDA Guidance for Industry, 2006, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production Back to Top 4. Can Total Organic Carbon (TOC) be an acceptable method for detecting residues of contaminants in evaluating cleaning effectiveness? Yes. Since the publication of the inspection guide on cleaning validation in 1993, a number of studies have been published to demonstrate the adequacy of TOC in measuring contaminant residues. We think TOC or TC can be an acceptable method for monitoring residues routinely and for cleaning validation. But in order for TOC to be functionally suitable, it should first be established that a substantial amount of the contaminating material(s) is organic and contains carbon that can be oxidized under TOC test conditions. This is not a trivial exercise because we know that some organic compounds cannot be reliably detected using TOC. TOC use may be justified for direct surface sample testing as well as indirect (rinse water) sample testing. In either case, because TOC does not identify or distinguish among different compounds containing oxidizable carbon, any detected carbon is to be attributed to the target compound(s) for comparing with the established limit. Thus, a firm should limit background carbon (i.e., carbon from sources other than the contaminant being removed) as much as possible. The established limit, or the amount of residue detected for comparison to the specification, should correct for the target material's composition of carbon. As for any cleaning method, recovery studies are necessary (21 CFR 211.160(b)). If TOC samples are being held for long periods of time before analysis, a firm should verify the impact of sample holding time on accuracy and limit of quantitation. References: Back to Top 5. Would a paramagnetic or laser oxygen analyzer be able to detect all possible contaminants or impurities in a medical gas? No. Although paramagnetic and laser oxygen analyzers are very accurate and reliable when calibrated correctly, these types of analyzers can only detect the presence and measure the strength of oxygen. They are unable to detect contaminants or impurities that may be present, such as hydrocarbons or arsenic compounds. The USP monograph test for oxygen does not include an impurity screen, and other analyzers may need to be used. For example, assays for hydrocarbon impurities are routinely conducted during the oxygen manufacturing process even though the USP does not list hydrocarbons as an impurity. Also, alternative methods may be needed to test high-pressure cylinders for cleaning solution residues. References: 21 CFR 211.160: General requirements (Laboratory Controls) 21 CFR 211.165: Testing and release for distribution USP Monograph: Oxygen USP Monograph: Oxygen 93 Percent Back to Top 6. Can up to 12-month expiration dating be assigned to oral solid and liquid dosage forms repackaged into unit-dose containers based on guidance in the May 2005 draft revision of Compliance Policy Guide Sec. 480.200 Expiration Dating of Unit Dose Repackaged Drugs (CPG 7132b.11)? No. In May 2005, a Notice of Availability of the draft revision of FDA’s Compliance Policy Guide Sec. 480.200 Expiration Dating of Unit-Dose Repackaged Drugs (CPG 7132b.11) was announced in the Federal Register. The draft CPG specifies certain conditions when it may be possible to assign up to 12-month expiration dating to nonsterile solid and liquid oral drug products repackaged into unit-dose containers without conducting new stability studies to support the length of expiration dating on the repackaged products. The draft CPG was prompted by USP standards for assigning up to a 12-month beyond-use date to nonsterile solid and liquid oral dosage forms dispensed in unit-dose containers. (Beyond-use date is USP’s pharmacy dispensing term for specifying a date on a prescription container beyond which a patient should not use the product.) If finalized, FDA’s draft CPG would replace the current version of CPG Sec. 480.200. The current version of CPG Sec. 480.200 was finalized in March 1995 and provides conditions under which FDA will not initiate action for assigning up to 6-month expiration dating for drug products repackaged into unit-dose containers without conducting new stability studies. FDA is conducting a stability study of certain commercially repackaged drugs to determine the suitability of the draft revision of CPG Sec. 480.200. Until the stability study is complete and FDA evaluates all comments submitted to the public docket in response to the May 2005 Federal Register Notice of Availability, the Agency does not intend to make a final decision on the draft revision of CPG Sec. 480.200. Consequently, at this time and until FDA announces a final decision on the draft CPG, the current CPG Sec. 480.200, which was finalized in March 1995, is in effect. References: Compliance Policy Guide Sec. 480.200 Expiration Dating of Unit Dose Repackaged Drugs (CPG 7132b.11) Draft Guidance on Expiration Dating of Unit-Dose Repackaged Drugs; Availability (70 FR 30953, May 31, 2005) 21 CFR 211.137: Expiration dating 21 CFR 211.166: Stability testing Back to Top 7. Is it ever appropriate to use an unvalidated method to test a drug component or product? The CGMP regulations require the use of validated methods when performing routine testing of raw material, in-process material, and finished products (21 CFR 211.160, 211.165(e), and 211.194) for manufacturing finished drug products. Method validation studies establish proof that a method is suitable for its intended purpose. The purpose is generally to measure a particular material’s conformance to an established specification (see the ICH guidance for industry Q2 (R1) Validation of Analytical Procedures: Text and Methodology). FDA recognizes, however, that test methods developed based on scientifically sound principles (e.g., sufficient accuracy and precision) but that are not fully validated may be suitable for use in certain instances during an investigation of a potential quality problem or defect. For example, investigation of an atypical impurity or possible contaminant of a drug product or any of its components (e.g., oversulfated chondroitin sulfate in heparin) may indicate the need for additional methods beyond routine quality control tests. Such testing may be critical to promptly and adequately evaluate the problem and protect public health. Full evaluation of a method’s robustness and reproducibility may not initially be feasible or appropriate when conducting tests in certain investigations. When a company, for whatever reason, tests drug components or products using an unvalidated method, it is important to recognize the possibility of greater uncertainty in the test results derived from these unvalidated test methods, as compared to validated test methods. Nevertheless, the resulting data may yield important information indicating the need for prompt corrective action. Accordingly, we expect all such test results on drug components or products to be reviewed to assess the need for follow-up action (21 CFR 211.192 and 211.180(e)). References: Date: 1/6/2011 Back to Top 8. Did FDA withdraw the 1987 Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices? Yes, FDA withdrew the 1987 Guideline. The 1987 Guideline is considered obsolete and does not reflect the Agency’s current thinking on the topic. Date: 7/12/2011 Back to Top 9. Where can drug manufacturers find information regarding endotoxin testing? USP publishes endotoxin testing recommendations and acceptance criteria in USP General Chapter Bacterial Endotoxins Test. General Chapter provides methods and calculation of limits for drugs. FDA may, as needed, provide additional guidance to clarify the Agency’s current thinking on use of Limulus Amebocyte Lysate (LAL), recombinant LAL, and other endotoxin testing methods. References: USP General Chapter Bacterial Endotoxins Test Date 7/12/2011 Back to Top 10. Is it acceptable to release non-penicillin finished drug products to market if the products may have been exposed to penicillin, as long as the non-penicillin products are tested and no penicillin residue is found? 21 CFR 211.176, Penicillin Contamination, allows marketing of non-penicillin finished drug products if they are tested using the codified method and found not to be contaminated with penicillin. However, it is not acceptable to release the product unless all other applicable CGMP requirements have been met. In some cases, firms inappropriately apply § 211.176 to market products that have not been produced under CGMP. Notably, 21 CFR 211.42(d) requires that manufacturing operations for penicillin drug products be performed in facilities separate from those used for non-penicillin human drug products. Similarly, 21 CFR 211.46(d) requires that air-handling systems for penicillin and non-penicillin drug products be completely separate. For example, if a non-penicillin product is made in a facility that shares equipment or an air-handling system with a penicillin production area (in violation of § 211.46(d)), the non-penicillin product cannot be made CGMP-compliant through testing alone. However, if a door is accidentally left open between a penicillin-dedicated area and other separate production areas, resulting in possible exposure of the other areas to penicillin, testing those other products for penicillin could justify their release for distribution. However, as per 21 CFR 211.165, all sampling plans and acceptance criteria used for testing and release of the non-penicillin product, including any testing for penicillin contamination, must be adequate to ensure the tested product meets all of its specifications. References: 21 CFR 211.176: Penicillin contamination 21 CFR 211.42(d): Design and construction features 21 CFR 211.46(d): Ventilation, air filtration, air heating and cooling 21 CFR 211.165: Testing and release for distribution Date: 6/17/2015 Back to Top 11. Can a facility that produced penicillin dosage forms be decontaminated and renovated for production of non-penicillin dosage forms, provided there is no further penicillin production in the renovated facility? Yes; however, decontamination can be extremely difficult. The decontamination process must include scientifically sound studies demonstrating the efficacy of the decontamination agents, extensive and statistically appropriate sampling throughout the areas before and after decontamination to verify cleanliness, and appropriate testing of such samples with a validated analytical method having an appropriate limit of detection. The CGMP regulations in 21 CFR 211.176 require that if a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin product must be tested for the presence of penicillin and cannot be marketed if detectable levels are found using the codified method. Such a reasonable possibility may be present if decontamination has not been conducted effectively. Although CGMP regulations do not prohibit decontamination and conversion, the difficulty of cleaning up penicillin residues can make the process daunting (see also FDA Guide to Inspections, referenced below). References: Date: 6/17/2015 Back to Top 12. Is there an acceptable level of penicillin residue in non-penicillin drug products? No. There is no established safe level of penicillin residue in non-penicillin drug products (see FDA guidance for industry, referenced below). The CGMP regulations in 21 CFR 211.42(d) and 211.46(d) require that penicillin-manufacturing facilities and air-handling systems must be adequately separated from those used to manufacture other drugs. 21 CFR 211.176 states that a non-penicillin drug product must not be marketed if penicillin is found when tested according to the codified procedure. Alternative validated test methods to detect penicillin residues may be used if demonstrated to be equivalent to or better than the referenced method. References: 21 CFR 211.176: Penicillin contamination 21 CFR 211.42(d): Design and construction features 21 CFR 211.46(d): Ventilation, air filtration, air heating and cooling FDA Guidance for Industry, 2013, Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination Date: 6/17/2015 Back to Top 13. For injectable drugs in multiple-dose containers, is the number of entries to withdraw a dose a factor in determining the expiration date? Generally, no. Unless the multiple-dose container is labeled to yield a specific number of doses of a stated volume, there is no limit to the number of withdrawals that may be made from a multiple-dose container before the drug is depleted or reaches its expiration date. The primary concern with multiple-dose containers is the potential for contaminating the product during multiple penetrations through the container stopper. Although the expiration date assigned to such products would be based on the stability of the drug product, stability protocols should include requirements for testing and evaluating container-closure integrity. Container-closure integrity testing may include physically testing the closure seal by using a leak test and monitoring the system’s ability to prevent microbial contamination. For multiple-dose injection product containers, functionality testing can include a self-sealing capacity test involving multiple penetrations of a hypodermic needle through the container stopper (see USP references below). Furthermore, injectable drug products in multiple-dose containers are generally formulated with an antimicrobial agent or preservative—or they contain inherently antimicrobial ingredients—and must meet requirements in accordance with the approved application (new drug application/abbreviated new drug application, biologics license application) and/or USP requirements. References: 21 CFR 211.166: Stability testing USP 38–NF 33 (2015) General Chapter Injections USP 38–NF 33 (2015) General Chapter Elastomeric Closures for Injections FDA Guidance for Industry, 1996, ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products FDA Guidance for Industry, 2003, ICH Q1A(R2) Stability Testing of New Drug Substances and Products FDA Guidance for Industry, 1996, ICH Q1C Stability Testing for New Dosage Forms FDA Guidance for Industry, 2013, ANDAs: Stability Testing of Drug Substances and Products FDA Guidance for Industry, 2014, ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers FDA Guidance for Industry, 2008, Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products Date: 6/17/2015 Back to Top 14. How long may a firm store in-process/intermediate powder blends and triturations, sustained-release pellets/beads, and tablet cores, absent separate stability studies, before using them in finished drug products? For in-process/intermediate materials that are chemically and physically stable, a risk- and science-based assessment process can help identify which material attributes and process parameters might affect the critical quality attributes of the finished drug product in which they are to be used. This assessment should be designed to ensure that materials held (under appropriate storage conditions) for a specified period are appropriate for use in manufacturing the finished drug product without having to conduct formal stability studies to verify the holding periods. In some instances, the risk assessment may include sampling and testing the material being held (at the stage determined by the risk assessment) to verify the manufacturing holding period. However, for unstable materials or for materials held longer than the period established in the risk assessment, firms should conduct stability studies according to an approved stability protocol to verify holding periods. The stability studies should include evaluations of the in-process/intermediate materials up to the time of their use in manufacturing a finished drug product and should include long-term monitoring of finished product batches manufactured with the in-process/intermediate materials. In the latter case, until appropriate stability data are generated, firms should calculate the expiration date assigned to finished product batches based on the date of manufacture/release of the in-process/intermediate material rather than on that of the finished product. References: 21 CFR 211.110: Sampling and testing of in-process materials and drug products 21 CFR 211.111: Time limitations on production Date: 6/17/2015 Back to Top 15. What material can be used as instrument calibration standards for chromatographic systems? For chromatographic systems, instrument calibration standards should be chosen from highly purified materials that are well characterized and can be accurately weighed. Standards can be compendial (from USP) or non-compendial (e.g., from NIST, a chemical supplier, or produced in-house). Substances obtained from a chemical supplier or produced in-house should be purified and characterized using validated purification processes and validated characterization methods. Purification is necessary because impurities can add variation and interfere with analytical methods. Finished dosage forms generally should be avoided as standards because excipients in the finished dosage form may interfere with analysis. References: FDA guidance for industry, 2015, Analytical Procedures and Methods Validation for Drugs and Biologics 21 CFR 211.160(b)(4): Instrument calibration 21 CFR 211.194(a)(2) and (c): Method validation and reference standards USP General Chapter Chromatography, section on System Suitability Date: 8/12/2019 Back to Top 16. What material can be used for system suitability? FDA expects system suitability to be checked using qualified primary or secondary reference standards and any materials necessary to ensure adequate method performance. A new batch of highly pure reference standard material (e.g., from a chemical supplier or produced in-house) should be qualified against the primary reference standard. Finished dosage forms or APIs that have not been qualified as reference standards should not be used for system suitability testing. Even when API or a finished dosage form has been properly qualified as a reference standard, it should not be used for system suitability testing if it is from the same batch as sample(s) being tested. Written procedures must be established and followed (21 CFR 211.160 and 211.194). All data — including obvious errors and failing, passing, and suspect data — must be in the CGMP records and subject to review and oversight. Records must be complete (e.g., 21 CFR 211.68(b), 211.188, and 211.194) and subjected to adequate review (21 CFR 211.68(b), 211.186(a), 211.192, and 211.194(a)(8)). References: FDA guidance for industry, 2015, Analytical Procedures and Methods Validation for Drugs and Biologics FDA guidance for industry, 2018, Data Integrity and Compliance With Drug CGMP: Questions and Answers USP General Chapter Chromatography, section on System Suitability Date: 8/12/2019 Back to Top 17. Is it ever appropriate to perform a “trial injection” of samples? No. FDA has observed at some drug manufacturers the practice of a trial injection where a sample of a lot is injected into the chromatographic system with the intention of obtaining an unofficial result (e.g., passing or failing). This is in contrast to the appropriate practice where an injection of a standard is performed with the sole intention of determining if the chromatographic system is fit for purpose. The injection of trial samples is not acceptable, in part, because all data from analysis of product samples must be retained and reviewed (21 CFR 211.22, 211.165, 211.192, and 211.194). Furthermore, uncertainty about system performance may also suggest a potential insufficiency of the method’s design, validation status, analyst training, equipment maintenance, or other fundamental problem(s) in the laboratory that should be promptly corrected. Column conditioning does not involve injecting a sample from a lot and is not considered a trial injection. When its use is scientifically justified, column conditioning should be fully described in the method validation package as to the conditions needed to make the measurement (i.e., based on data from the method validation) and should be clearly defined in an approved and appropriate procedure. Only validated test methods that demonstrate accuracy, sensitivity, specificity, and reproducibility may be used to test drugs (21 CFR 211.165(e)). Consistent and unambiguous injection nomenclature should be used, and all data from the column conditioning, including audit trail data, should be maintained and subject to review. Therefore, FDA considers it a violative practice to perform a trial injection (including under the guise of column conditioning). FDA also considers it a violative practice to use an actual sample in test, prep, or equilibration runs as a means of disguising testing into compliance. References: FDA guidance for industry, 2015, Analytical Procedures and Methods Validation for Drugs and Biologics 21 CFR 211.194(a)(2): Method validation Date: 8/12/2019 Back to Top Contact for further information: CDER-OPQ-Inquiries@fda.hhs.gov Home | General Provisions | Buildings and Facilities | Equipment | Control of Components and Drug Product Containers and Closures | Production and Process Controls | Holding and Distribution | Laboratory Controls | Records and Reports | Returned and Salvaged Drug Products

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