Sampling Plans for Quality Audits

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FDANEWS

Topics

- Overview of a Quality Audit
- ISO 19011:2018
- Sampling Approaches to an Audit
- Statistics of Sampling
- Compliance Tests
- FDA Device Inspections
- Summary and Conclusions
- Questions

Overview of a Quality Audit

Data Collection and Analysis

- The auditor's task is to:
  - Collect factual audit evidence using the sampling method
  - Analyze that evidence
  - Evaluate the evidence against the audit criteria
  - Draw conclusions from the evaluation
  - Generate audit findings

Audit Evidence

- The auditor obtains evidence from two primary sources:
  - Interviews of people involved in the process
  - Records generated by the process

- Sampling methods apply to evidence obtained from records

Procedures and Records

- Documented procedures, work instructions, and drawings provide information on how to perform a process in a consistent manner.

- Records are a particular kind of document that provide objective evidence that activities have been performed or results have been achieved.

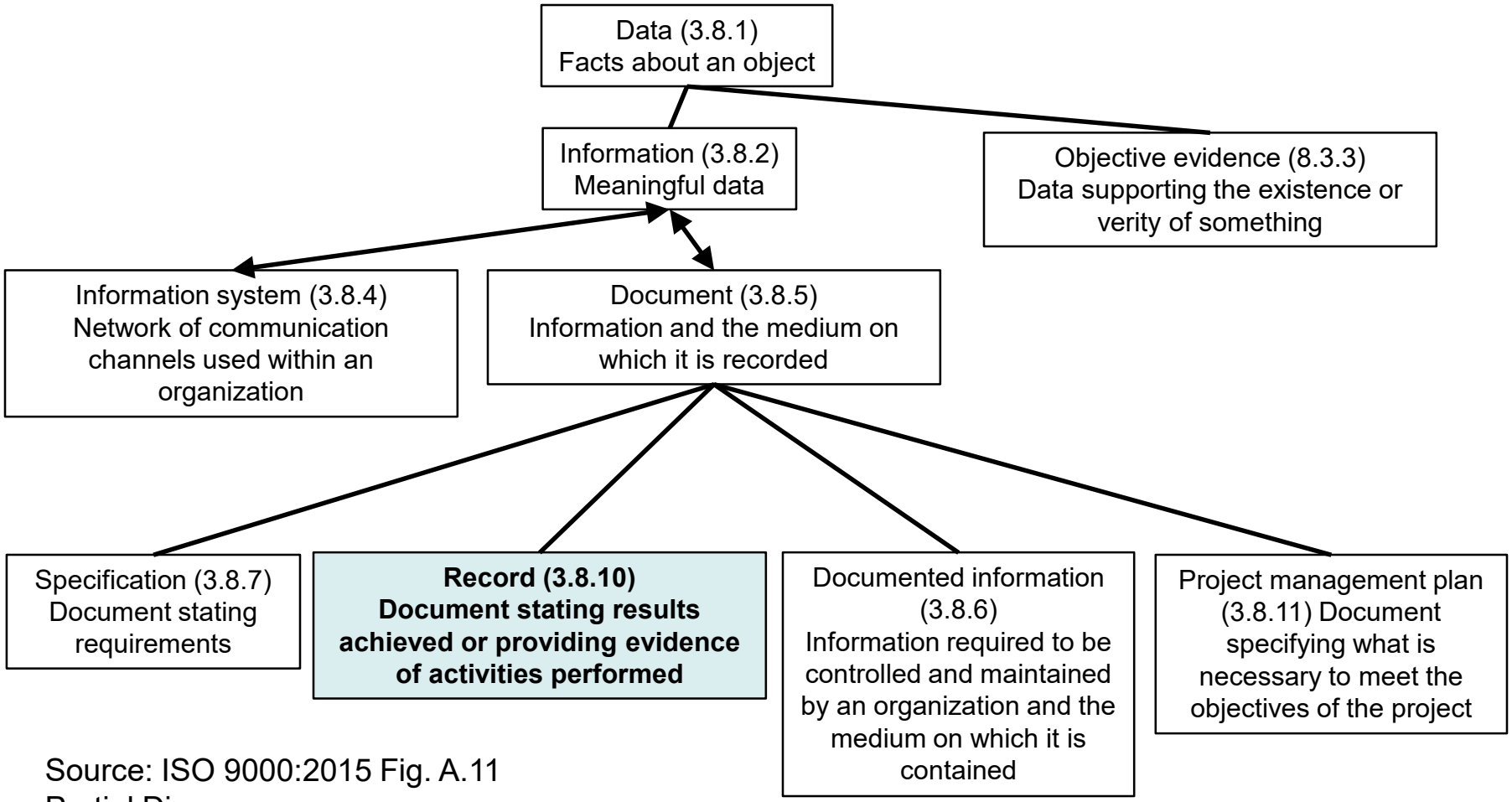
Records

- ISO 9000:2015, 3.8.10 provides a definition for a record
  - *Record* means a document stating results achieved or providing evidence of activities performed.

- Because ISO 13485:2016 cites ISO 9000:2015 as a normative reference, this definition applies

- FDA QSR does not define a record, but uses the term extensively

Date, Information, and Document Concepts



Source: ISO 9000:2015 Fig. A.11
Partial Diagram

Control of Records

- Following ISO 13485:2016, clause 4.2.5, a company should control two kinds of records:
  - Records established to provide evidence of conformity to requirements
  - Records established to provide evidence of the effective operation of the quality management system

Control of Records

- Following ISO 13485:2016, clause 4.2.5, create documented procedures for record control including:

Identification	Storage	Protection
Retention	Retrieval	Disposition

- Records must:
  - Remain legible
  - Be readily identifiable
  - Be retrievable

ISO 19011:2018

ISO 19011:2018

- ISO 19011:2018 *Guidelines for Auditing Management Systems*
- Annex A Additional guidance for auditors planning and conducting audits
- Annex A.6 Sampling

Audit Sampling Steps

- Annex A.6.1 provides steps for audit sampling
  - Establish the objectives of the sampling plan
  - Select the population to be sampled
  - Select the sampling method
    - Judgement or Statistical
  - Determine the sample size
  - Conduct the sampling
  - Compile, evaluate, document, and report the results
    - The report should include a description of the population, the sampling method, the size, estimates based on the sample, and the confidence level

Judgement Samples

- Annex A.6.2 discusses judgement sampling
  - Relies on the knowledge, skill, and experience of the audit team

- Considerations include:
  - Previous experience with the audit scope
  - Complexity of the requirements to meet the audit objectives
  - Complexity of the processes and the quality management system
  - Previously identified areas of risk
  - Previously identified areas of improvement

- Judgement samples don't provide a statistical estimate of the audit findings

Statistical Samples

- Annex A.6.3 discusses statistical sampling
- Use probability methods for the sample selection method
  - Attribute sampling for pass/fail, conforming/nonconforming, *etc*.
  - Variables sampling when the sample outcomes are continuous values

- Sampling plans depend on the risk the auditor is willing to accept
  - This is usually called the acceptable confidence level
  - For example, a sampling risk of 5% corresponds to an acceptable confidence level of 95%

- The reported results should include:
  - A description of the population sampled
  - The sampling criteria used the evaluate the sample
  - The statistical parameters and methods
  - The number of samples evaluated
  - The results

Sampling

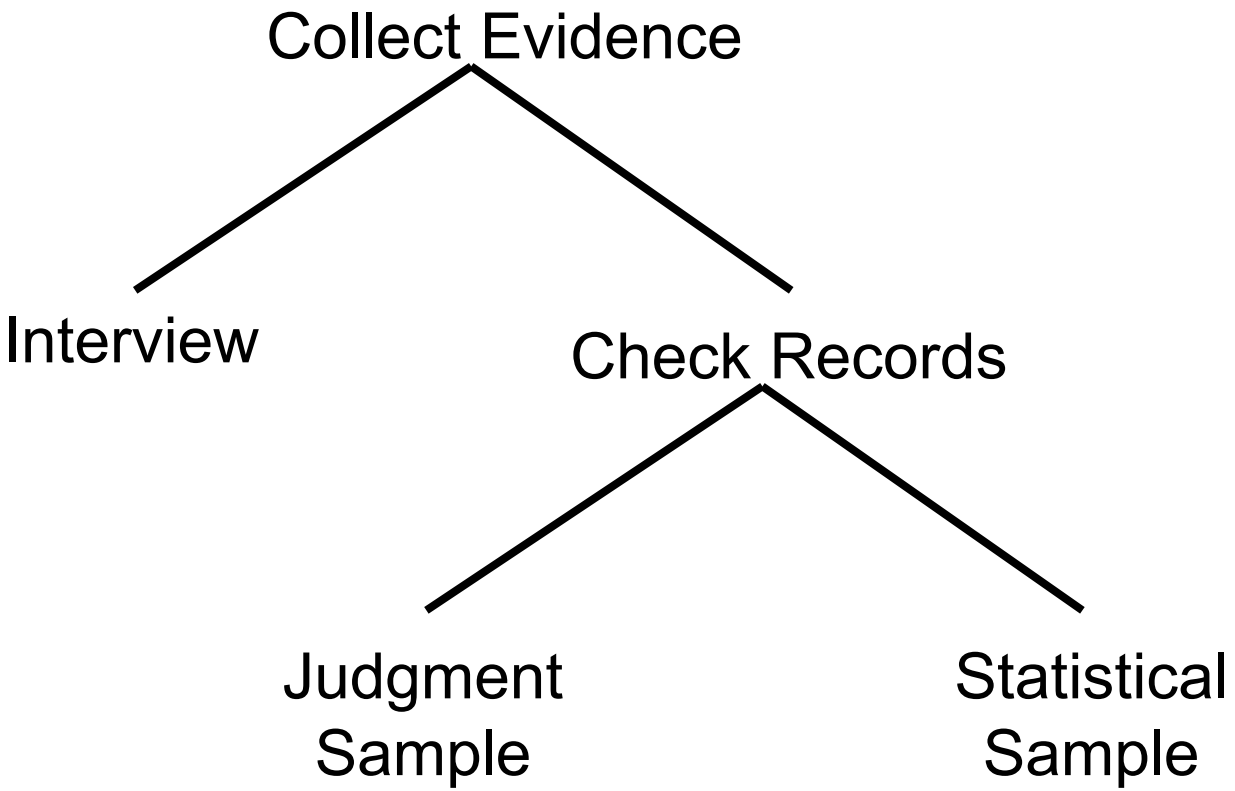
Tracing

- Tracing follows a process:
  - Forward tracing moves “downstream”
  - Backward tracing moves “upstream”
  - The Auditor could start in the middle and trace in either direction

- Tracing establishes that the process and procedures operate as described

- Unannounced visits for the EU-MDD often use backward tracing product audits starting with final acceptance

Audit Overview



Judgment Samples

- Judgment samples don't use statistical methods
- The advantage is that judgment samples can often provide a "sense" of the process without a lot of work
  - Judgment samples tend to be smaller
- The disadvantage is that judgment samples don't allow the quantification of the results
  - Statistical samples tend to be larger

Judgment Samples

- Judgment sampling relies on the knowledge, skills, and experience of the audit team.

- A drawback to judgment sampling is the lack of a statistical estimate of the effect of uncertainty in the findings of the audit and the conclusions reached.

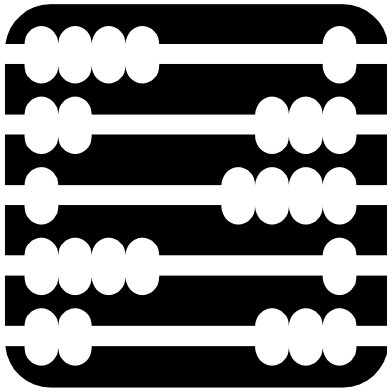
Compliance Tests

- Compliance tests show that process operation is satisfactory.
  - These tests determine whether process control is effective by counting the number of nonconforming records

- Compliance tests use sampling methods
  - Judgment samples may be acceptable
  - Statistical samples may be required (especially for critical processes)

Contrasting the Methods

Tracing is an audit method to follow the process, a process walk through. Tracing usually follows the process using procedures, flow charts, *etc*.



Compliance tests check the records for existence, correctness, completeness, *etc*. based on the procedures and flow charts.

Statistics of Sampling

Binomial Distribution

Confidence Intervals

Judgment Samples

- Judgment samples rely on the knowledge and experience of the auditor
- The Lead Auditor says to the audit team, “When you use judgment samples, look at 3, 5, 7, or 11 records.”
- One team member asks why, and the Lead auditor responds, “I really like prime numbers”.

The Binomial Distribution

The Bernoulli Trial

- Bernoulli trials are a sequence of *n* independent trials, where each trial has only two possible outcomes.

- Example – Flip a coin fifty times
  - This is a sequence of trials
  - *n = 50*
  - The trials are independent, because the coin doesn't "remember" the previous trial
  - The only outcome of each trial is a head or a tail

The Binomial Distribution

- The Bernoulli trial has two possible outcomes.
  - One outcome is “success” with probability *p*.
  - The other “failure” with probability *q* = *1* – *p*.

- The binomial distribution is the probability of *x* successes in *n* trials

$$\Pr(x) = \binom{n}{x} p^x (1-p)^{n-x},\ x = 0, 1, \cdots, n$$

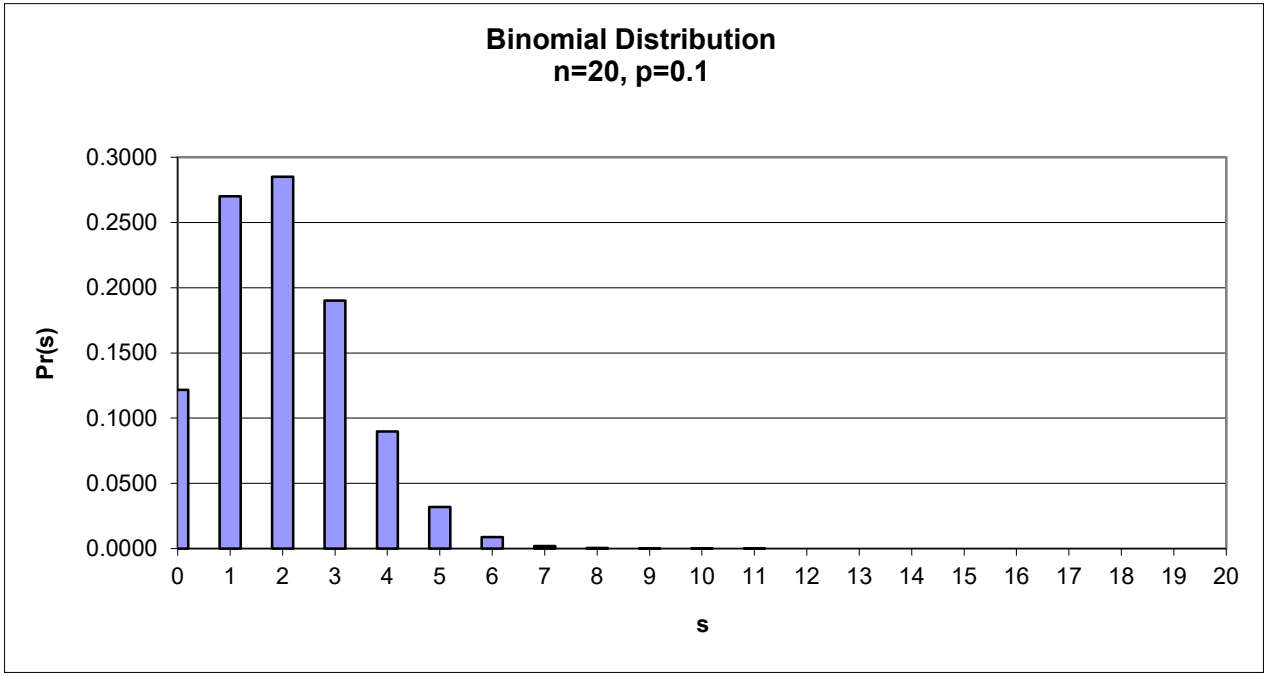
Excel Example

s	Pr(s)
0	0.1216
1	0.2702
2	0.2852
3	0.1901
4	0.0898
5	0.0319
6	0.0089
7	0.0020
8	0.0004
9	0.0001
10	0.0000
11	0.0000
12	0.0000
. . .	. . .
20	0.0000

n = 20, p = 0.1

What is the probability of exactly 0 successes, 1 success, *etc*.

BINOMDIST(number_s,trials,probability_s,cumulative)



Counting and Classifying Records

Records

- An auditor examines a certain number of records
  - Could be a judgment sample
  - Could be a statistical sample – a conformance test

- Typically, the audited process generates records at specific points as described in the procedure or process flow.

- Example: The record uses a form on one sheet of paper with 10 fields to complete.

Count & Classify

- In our example, each record is a one page form with 10 fields.

- To continue the example, assume the auditor looks at seven records with the following results:
  - #1 All fields are correct
  - #2 Field A has a nonconformance
  - #3 All fields are correct
  - #4 Field A has a nonconformance
  - #5 Fields E and G each have a nonconformance
  - #6 All fields are correct
  - #7 All fields are correct

Count & Classify

- How many nonconforming records are in the sample?
  - There are three nonconforming records, #2, #4, & #5
- What is the point estimate of the nonconformance rate?
  - There are 3 nonconforming records out of 7 or 3/7 = 0.429 or 42.9%
- How many opportunities for error are in the sample?
  - There are 7 records, each with 10 fields or 7×10 = 70
- How many nonconformities are in the sample?
  - Two records have one nonconformity and one record has two for a total of 1+1+2 = 4
- What is the rate of nonconformities?
  - 4 nonconformities in 70 opportunities or 4/70 = 0.057 which is 5.7% or 57,000 parts per million

The Auditing Convention

- In audit sampling, count the number of nonconforming records, not the number of nonconformities.

- Every record should be correct, so a record with one nonconformity and one with five nonconformities, counts the same!
  - Each represents one nonconforming record

The Bernoulli Trial

- Notice that we have a Bernoulli Trial
- Each record can have only two outcomes, conforming or nonconforming
- Each record reviewed is independent of all the others, *i.e.,* the records don't "remember" each other
- The auditor is working on the nonconformance rate, so a nonconforming record is a "success"
  - Since the audit looks for nonconforming records, each one found is a "success" in the language of the binomial distribution

Process Improvement Convention

- In process improvement, we are more likely to count nonconformities and their location.
- For example, we have 4 nonconformities in 70 opportunities.
- We could also construct a Pareto analysis to show the results

Compliance Tests

Objective

- A compliance test can establish the frequency of failure to comply with the process or system
- The compliance test can establish the extent of errors
- The compliance test helps determine if the process and procedure is effective and if the operations are conducted effectively

Maximum Tolerable Error Rate

- If the auditor could look at every record, then the occurrence rate of errors could be stated exactly.
  - 2.76% of purchase orders did not have the correct authorizing signature based on the dollar value
  - 1.16% showed acceptance of an out of specification result

- There is a point where, if the failure rate is too high, the company must take action. This is the *maximum tolerable error rate* (MTER).

The MTER

- The MTER could differ based on the importance of the process or the criticality of the record.

- The MTER is not a precise figure, but a zone.
  - An error rate of 3.76% is acceptable but 3.77% requires action
  - Instead, consider that an error rate in the vicinity of 3.75% requires action

- Some actions, such as fraud, deliberate misstatements of results, or falsified records are intolerable; the MTER is 0.0%.

Sampling and the MTER

- We could define a sample based on the MTER.
- Ask the question, “What sample size do I need so I’m confident that the error rate is below 5% when I don’t find any nonconforming items in the sample.”
- We could ask the question for 1 nonconforming item, 2 nonconforming items, *etc*.

Confidence

- We could compute a point estimate for the sample.

- We have a sample of 150 records and classify 12 of them as nonconforming.
  - The point estimate is 12/150 = 0.08 or 8.0%

- What can we say about the whole population?
  - The error rate is inside some bound
  - For example we could say with 95% confidence, that the true error rate is between 3.7% and 12.3%.

A Common Plan

- A very popular sampling plan is:
  - The MTER is 5%
  - Sample size is 60
  - If the number of nonconforming records is 0
  - The limit is 4.9% at the 95% confidence interval

- If we have a sample of 60 records and don't find any nonconforming, we can say the true error is less than 4.9% with 95% confidence.

- In this case, we have a valid conclusion that completes the compliance test.

Calculations in Excel

- Appendix A shows how to do this calculation in Excel.
- Using the Excel method you can calculate the upper confidence interval for any combination of sample size and nonconforming units.

Another Version

- In the previous case, we had zero (0) nonconformances.
- We could achieve the same result in other ways
- A sample size of 100 and 1 error gives a true error of less than 4.7% with 95% confidence.

FDA Inspections

QSIT

- FDA Inspections of device manufacturers use the Quality System Inspection Technique (QSIT).

- The QSIT is a top down approach to the inspection.
  - It starts with the documents, procedures, and work instructions that define specified subsystems
  - It “gets to the bottom” by examining records

QSIT is a Compliance Test

- In an FDA Inspection, the Investigator conducts a compliance test.

- The Investigator starts with the subsystem:
  - Management Controls
  - Design Controls
  - Corrective and Preventive Actions (CA&PA)
  - Production and Process Controls (P&PC)

- The Investigator will examine records using the QSIT sampling plan

Sampling Plan Instructions

1. Select the table based on the confidence interval desired. For example, if you are reviewing Device History Records of a life supporting device, you may choose to use Table 2 (99% Confidence). You may choose to use Table 1 (95% Confidence) for the review of Device History Records regarding a device with lower risk.

2. Select a sample size. If the population of records to be sampled is small (approximately thirty or less), you may choose to review all of the records.

3. Review the sample of records selected. You can terminate your review of the entire sample if you observe objectionable conditions beyond the number stated in the column header.

Note: There are no “acceptable” violations of the Quality System Regulation. When using the “1 out of:” and “2 out of:” columns, it does not mean no more than that number of Quality System Regulation violations per the appropriate sample size is acceptable. It will only give you an initial understanding of how prevalent the problem may be.

Table 1 – 95% Confidence

Row	Limit	0 out of:	1 out of:	2 out of:
A	0.30	11	17	22
B	0.25	13	20	27
C	0.20	17	26	34
D	0.15	23	35	46
E	0.10	35	52	72
F	0.05	72	115	157

Table 2 – 99% Confidence

Row	Limit	0 out of:	1 out of:	2 out of:
A	0.30	15	22	27
B	0.25	19	27	34
C	0.20	24	34	43
D	0.15	35	47	59
E	0.10	51	73	90
F	0.05	107	161	190

Example

- An auditor uses the QSIT tables during an internal quality audit.
- The auditor determines the process is not critical, and could tolerate an error rate of 15%
  - Because the process is not critical, the auditor uses the 95% table.
  - The auditor uses

    Table 1 Row D Column “0 out of:”
  - This leads to a sample size of 23, *i.e.,* examine 23 records
  - If the auditor doesn’t find any nonconforming records in the sample of 23, she can make a statistical statement
- The auditor concludes that, with 95% confidence, the process error rate is less than 15%

Example Continued

- Assume the same situation as before, Table 1, Row D.
- At the 17th record, the auditor finds a nonconforming record.
- The auditor continues to sample the records. After 35 records, the auditor found only one nonconforming record.
- The auditor concludes the process meets the compliance test:
  - Table 1
  - Row D
  - Column “1 out of:”

Notice the change in columns because of the nonconforming record

Warning Letter
Fall Prevention Technologies
August 27, 2008

The firm manufactures a device intended for recording, viewing, and analyzing eye movements in support of identifying balance disorders in human patients.

Failure to review associated data and documentation for all finished devices before they are released for distribution, as required by 21 CFR §820.80(d)(2).

For example, **5 of 11 of the finished iVNG device history records reviewed** by the investigator revealed that the devices had been released prior to written approval.

Presumably, the Investigator used Table 1 95% Confidence, Row A (0.30), and Column "0 out of:"

This is the only case where the sample size is 11.

Warning Letter
Measurement Specialties, Inc.
October 12, 2011

- The firm manufactures temperature probes for pediatric and adult use.

- Specifically, your firm is not analyzing nonconformances found during finished device assembly based on a statistical methodology that will detect recurring quality problems. **A total of 9 of the 11 device history record reviewed** had the reasons for the nonconformances during finished device assembly that were dispositioned as scrap recorded, but this data is not being analyzed based on a statistical methodology to detect recurring problems.

Presumably, the Investigator used Table 1 95% Confidence, Row A (0.30), and Column “0 out of:”

This is the only case where the sample size is 11.

Warning Letter
Acme Monaco Corporation
April 28, 2014

The firm manufactures medical guidewires for cardiovascular and urologic use

You have not established procedures for device history records. Specifically, a sample of these records was reviewed during the inspection; **40% (6 of 15) of the records were not properly documented**, either lacking required information or containing incomplete information.

Presumably, the Investigator used Table 2, 99% Confidence, Row A (0.30), and Column “0 out of:”

This is the only case where the sample size is 15.

Warning Letter
Augusta Medical Systems, LLC
January 12, 2012

Failure to ensure that each production run, lot, or batch of finished devices meets acceptance criteria, as required by 21 CFR §820.80(d).

Specifically, during our inspection it was determined that the Pump Head Final Inspection Sheets for the following lots of Response II and Touch II devices photocopied from an unknown production record … As a result, the device history records for these lots do not ensure that each of these finished devices met the acceptance criteria identified in your procedure titled "Final Inspection for Battery and Manual Pump Heads".

In checking the records the Investigator observed photocopies of an unknown record. This raises a question about the test of the units.

Summary

Summary

- A quality audit typically follows a process
  - A process can be traced forward or backward
- The auditor collects objective evidence by
  - Conducting interviews
  - Examining records
- The records can be sampled using a
  - Convenience sample
  - Statistical sample

Summary

- Statistical samples allow compliance tests
  - Compliance tests can help determine how well the process meets its requirements
  - Compliance tests often use the Maximum Tolerable Error Rate (MTER)

- The MTER can be converted to a sampling plan

- The FDA QSIT uses this technique for inspections of medical device manufacturers

QUESTIONS

Appendix A
Excel Calculations

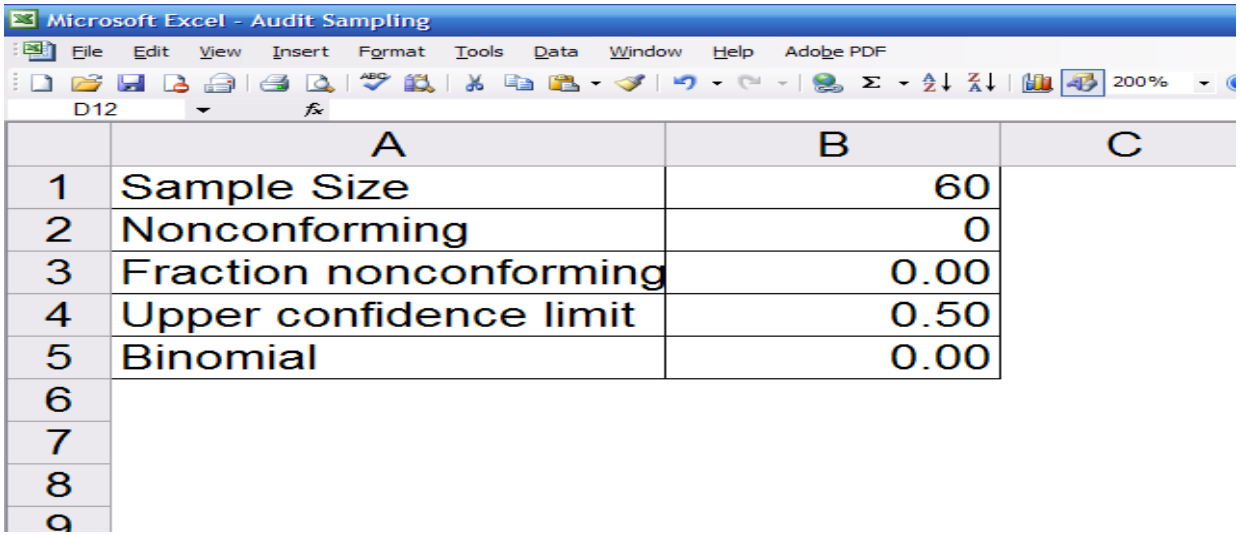
Exact Values

- There is method to estimate the confidence interval of the binomial distribution using the Normal distribution

- That estimate is not suitable in this case, but Excel can provide an exact value.

The Set Up

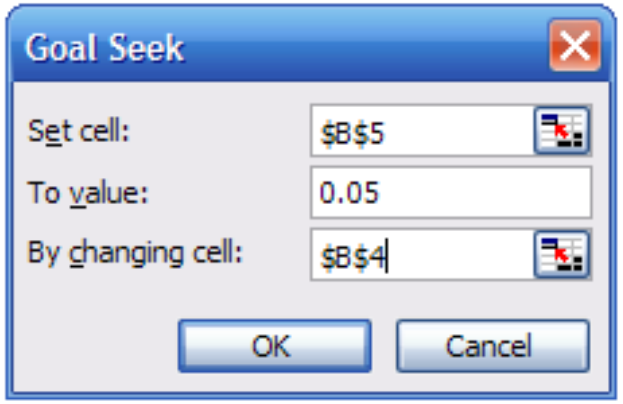
- Set up an Excel worksheet as shown below.
  - The formula in cell B3 is =$B$2/$B$1
  - The formula in cell B5 is =BINOMDIST($B$2,$B$1,$B$4, TRUE)



	A	B	C
1	Sample Size	60	
2	Nonconforming	0	
3	Fraction nonconforming	0.00	
4	Upper confidence limit	0.50	
5	Binomial	0.00	
6			
7			
8			
9			

Use Goal Seek

- Use goal seek to determine the upper confidence limit
- The “To value:” is 0.05 which comes from the 95% confidence interval
- Clip OK and the upper confidence limit, in cell B4, becomes 0.049



The QSIT Tables

- You will get different results if you do these calculations to duplicate the QSIT tables
- The QSIT were calculated using both upper and lower confidence values
- For an audit, we are concerned with the upper confidence limit only