



CEMD 0920

Salt Lake
Community
College 

Basic Manufacturing Skills Week 1



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Medical Device Training Program Overview

- Department of Labor (DOL) TAACCCT grant: Community College Consortium for Bioscience Credential (CCCBC)
 - Develop accelerated career oriented training program (8-wk & 24-hr per course)
 - Cover knowledge & skills recognized by the medical device and biosciences industry nationwide.
 - Offer core skill and stackable certificates with transferability to education pathway (AS & AAS)

It's New !!

- New training program: Spread the word!!!
- Certificate award-industry recognized:
 - Core Skill Certificate- completion of 4 courses
 - Advanced subspecialty certificates (Quality, Auditing, etc.) – under development
 - Articulation of the Core Certificate to credits towards an Associate of Applied Science (AAS) or Associate of Science (AS) degree in Biotechnology – upon request
- Feedback appreciated

Course Description

- 8 week short intensive training; total 24 hours; 3 lecture & lab hours per week
- Provide core knowledge & skills required in a medical device or bioscience manufacturing environment
- Focus on:
 - Basic manufacturing activities and processes
 - Proper application of basic measurement tools
 - Safe & controlled environmental manufacturing behavior
 - Basic quality concept and critical thinking skills
 - Proper data collection, documentation & analysis

Early 1900's

1906 – The Food and Drugs Law

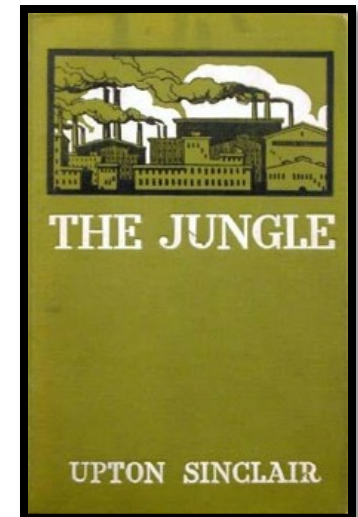
- medical devices are classified as drugs
- focus of the 1906 law was on labeling so devices essentially ignored

1906 - 1938

- Awareness grows that 1906 law is obsolete as public anger erupts over various drug toxicities such as Lash Lure and Radithor - but Congress fails to act

Sulfanilamide incident of 1937

- Over 100 dead, mostly children due to use of “antifreeze” in cough syrup because no testing or pre-approval was required by the 1906 law



1938 - Food, Drug, and Cosmetic Act

- Drugs must be proven safe AND effective before they can be sold...but not medical devices.
- FDA can only police devices after they are on the market and shown to be dangerous or not effective.

Quack Devices

Prior to 1960s FDA's efforts on devices is mostly to remove "quack" devices from market

- Orgone Accumulator
- Ruth B. Drown's Radio Therapeutic Instrument
 - Court documents revealed that four years after one woman faithfully used the radio instrument, she died of the very cancer that Ruth B. Drown's machine claimed to diagnose and cure.



Thalidomide Tragedy

- Sleep medication
- Marketed as “completely safe” including mother and child, “even during pregnancy,” as its developers “could not find a dose high enough to kill a rat.”
 - US FDA didn’t approve due to lack of testing
 - Europe and other parts of the world were less strict and allowed
 - By 1960, thalidomide was marketed in 46 countries, with sales nearly matching those of aspirin.
- Clinical trials didn’t need FDA the US even though it wasn’t marketed to public
 - hundreds were pregnant out of the thousands in the trail
- Initiated stringent FDA controls, especially for pregnant women
- Phocomelia, resulting in shortened, absent, or flipper-like limbs
- Australian Dr. William McBride
 - Discovered drug alleviated morning sickness.
 - Recommending **off-label use** to his pregnant patient
- Off-label
 - off-label, or purposes other than those for which the drug was approved,
 - is still a common practice in many countries today, including the U.S. In many cases, these off-label prescriptions are very effective, such as prescribing depression medication to treat chronic pain.



The 1970's

1972 - 1973

- Congress debates on regulations for medical devices but does not act

1974

- The Dalkon Shield debacle alters the landscape of medical device regulation in the U.S.
- Hearings take place on problems that had been reported with the Dalkon Shield intrauterine device, which caused thousands of reported injuries
- Thalidomide tragedy from the 1960s stands in contrast and highlights the value of prior approval based on safety and efficacy

1976

- Medical Device Amendments signed into law by President Ford
 - The 1976 amendments defined devices similarly to drugs, but noted that drugs cause a chemical reaction in the body, whereas devices do not. They called for all devices to be divided into classes, with varying amounts of control required in each one.

Major Effects of the 1976 Amendments...

- **1976** – Medical Device Amendments had 3 MAJOR impacts on medical devices...and on you if you want to work in a medical device company:
- medical devices receive their **own definition** that distinguishes them from drugs
- medical devices must be **proven safe and effective PRIOR** to marketing approval
- Good Manufacturing Practice (**GMP**) regulations are required for medical devices

Medical Devices - Keep Your Perspective!

- Why does the history of Medical Device regulation matter?
- Because dealing with government regulation is often boring and frustrating
- BUT! There are very good reasons to turn our attention to the details of medical device manufacturing skills and requirements

The regulations are the result of past tragedies we don't want...

"The first time I ever had occasion to call in a doctor for [Joan] and she was given Elixir of Sulfanilamide. All that is left to us is the caring for her little grave. Even the memory of her is mixed with sorrow for we can see her little body tossing to and fro and hear that little voice screaming with pain and it seems as though it would drive me insane. ... It is my plea that you will take steps to prevent such sales of drugs that will take little lives and leave such suffering behind and such a bleak outlook on the future as I have tonight."

- A woman describing the death of her child from sulfanilamide poisoning to President Franklin D. Roosevelt

The Focus on Quality in Manufacturing Medical Devices

- The authorization of Good Manufacturing Practice in the 1976 Amendments had a major impact on medical device design and manufacturing.
- Over time, this has become the central principle for all activities in designing and making a medical device

[How do I know if my product is regulated by FDA?](#)

Medical Device Development Process

- Prototype Design and Development
 - Preclinical Development
 - Trials Proof of Concept
 - FDA Approval Market Launch
 - Sustaining Engineering

Quality Based System

- **The QMS**
 - **Quality Management System**

Governs all of these components to ensure that Quality Based Design is being used

- **Planning**
 - **Quality Plan**
 - **Requirements**
- **Creation**
 - **Design**
 - **Prototyping**
 - **Evaluation**
- **Verification and Validation**
 - **Fabrication**
 - Testing**

Quality System (QS)-FDA

- By law (21 CFR 820) a company is required to have the following components as part of their Quality system
 - Management
 - Design Controls
 - Material Controls
 - Corrective and preventive Actions
 - Production and Process Controls
 - Equipment and facility controls
 - Records, Documents and Change controls

How Do You Avoid These Guys?

- **With good documentation practices!**
- **It is the only way to show compliance with the law!**



What do medical device companies get in trouble for?

- The main way that other companies can learn specifically how FDA is enforcing the Quality guidelines is by reading warning letters on the FDA website

[FDA Warning letter Database](#)

Most medical device companies get in trouble for documentation.

Top 10 citations of 2013

Frequency of Warnings	Ref no.	Short description
378	21.cfr.820.100 (a)	Procedure for corrective and preventive action have not been adequately established
245	21.cfr.820.198 (a)	Procedure for receiving, reviewing and evaluating complaints have not been adequately established
133	21.cfr.820.100 (b)	Corrective and preventive action activities and/or results have not been adequately documented
127	21.cfr.820.75 (a)	A process whose results cannot be fully verified by subsequent inspection and test has not adequately validated according to established procedures
124	21.cfr.820.17	Written MDR procedures have not been developed/maintained/implemented
110	21.cfr.820.50	Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been adequately established
98	21.cfr.820.90 (a)	Procedures have not been adequately established to control products that does not conform to specified requirements
93	21.cfr.820.30 (i)	Procedure for design change have not been adequately established
77	21.cfr.820.181	A device master record has not been maintained
73	21.cfr.820.22	Procedures for quality audits have not been adequately established

Manufacturing Basics: The Components of Manufacturing

- **Raw materials - Materials that will be modified by the manufacturing activity**
 - **Basic**
 - Sand
 - Water
 - Oil
 - Coal
 - **Complex**
 - Circuit Boards
 - Chemical compounds
 - Subassemblies
- **Manufacturing activity – Consumption of time and energy to alter raw materials for the purpose of adding value**
 - Governed by documentation
- **Verification - Determining correctness of the newly created result of the manufacturing activity by comparing to a known standard**

Material Traceability-QS, cGMP, GDP

- Unique code applied to each batch of raw materials
 - Identifies ingredients
 - Lists processing parameters and values
 - Includes dated signatures of responsible individual
 - Assists in preventing material from being used incorrectly
 - Follows the raw materials all the way through processing
- Device History Record (DHR)
 - Used to identify root cause of problems

Part numbers/Lot numbers/Revisions-QS, cGMP, GDP

- Part numbers
 - Define the characteristics of the item
 - Drawings and/or specifications
 - Used as a locator to find the item in the database
- Lot numbers
 - Segregate large batch into manageable quantity
 - Assigned to date-sensitive materials for production scheduling
- Revisions
 - Track changes to the item
 - Maintain traceability of part number

Bill of Materials (BOM)--QS, cGMP, GDP

- For every medical device manufacturing activity the BOM will list of items required to perform the activity
 - Part numbers
 - Revision level
 - Lot numbers
 - Quantity
 - Order that the raw materials are needed (indented BOM)
 - Tools and equipment
 - Can be on paper or in electronic format

Bill of Materials (BOM)--QS, cGMP, GDP Cont.

- BOM should include
 - BOM level
 - Part number
 - Part name
 - Phase
 - Description
 - Quantity
 - Unit of Measure
 - Procurement type
 - Reference designators
 - BOM notes

An accurate BOM supports efficient manufacturing processes.

Manufacturing Process (MP)-- QS, cGMP, GDP

- Recipe for performing the manufacturing activity
 - Work Instruction Document (WID) and Standard Operating Procedure (SOP) are more common names for the recipe
 - Contains BOM
 - Lists the order in which the activity must be done
 - May contain special instructions or comments
 - Includes in-process inspection instructions
 - Locations for data entry
- Controlled by document number and revision level
- Operator must be trained before performing

Verification vs Validation

- Verification
 - Comparison of design output with design input.
 - Are we building the system right?
- Validation
 - Determining that the product developed meets the customer's needs.
 - Are we building the right system?

Medical Device manufacturing requires the use of precision measurements

Precision instruments are important in all three components of the manufacturing process:

- raw materials
- manufacturing activities
- verification



Correct use of precision instruments requires an understanding of significant digits

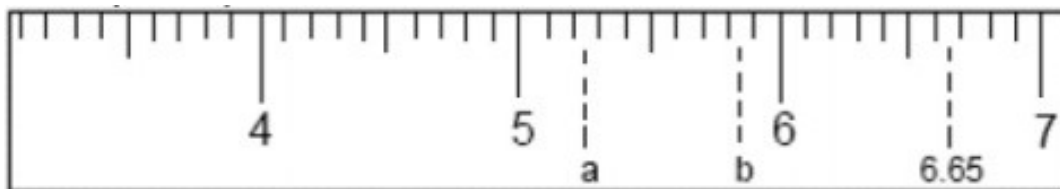
- There are two kinds of numbers in the world:
- **Exact:**
 - example: There are exactly 12 eggs in a dozen.
 - example: Most people have exactly 10 fingers and 10 toes.
- **Inexact:**
 - example: any measurement.
If I quickly measure the width of a piece of paper, I might get 22 mm (2 significant figures). If I am more precise, I might get 21.6 mm (3 significant figures). An even more precise measurement would be 21.56 mm (4 significant figures).

Accuracy vs Precision

- Accuracy
 - The degree of conformity to a standard or true value.
- Precision
 - The smallest repeatable digit of a measurement.
- Significant figures are the repeatable digits and the first uncertain digit in a measurement or calculation.

Significant Digits and Uncertainty

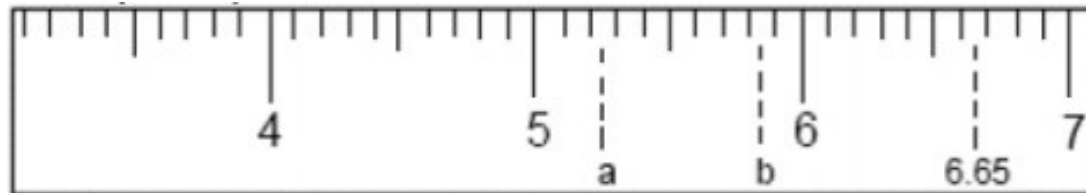
- The number of significant figures is the number of digits believed to be correct by the person doing the measuring. It includes one estimated digit.



- On the enlarged ruler above, the closest marks are 0.1 cm apart, so you can estimate to the hundredths place, (0.01 cm), but when looking at a metric ruler in the real world, the smallest marks (millimeter marks, mm) are so close that it is all we can do just to determine that the dotted line is between two of them - about half way.

Significant Digits and Uncertainty Cont. 1

- The dotted line to the right of the ruler is at a length of 6.65 cm. The last decimal place, the hundredth's place, in the measurement is estimated.



- Your best estimate of the position of the dotted line is 6.65 cm. We can say that the measuring instrument is readable to ± 0.05 cm. The ± 0.05 cm means that your measurement may be off by as much as 0.05 cm above or below its true value. This value is called the uncertainty or the precision of the instrument.

Significant Digits and Uncertainty Cont. 2

- The number of significant digits in an answer to a calculation will depend on the number of significant digits in the given data.
- When are Digits Significant?
 - Non-zero digits are always significant. Thus, 22 has two significant digits, and 22.3 has three significant digits.
- With zeroes, the situation is more complicated...

Significant Digits and Uncertainty Cont. 3

- Zeroes placed before other digits are not significant; 0.046 has two significant digits.
- Zeroes placed between other digits are always significant; 4009 kg has four significant digits.
- Zeroes placed after other digits but behind a decimal point are significant; 7.90 has three significant digits.
- Zeroes at the end of a number are significant only if they are behind a decimal point as in 7.90 (above). Otherwise, it is impossible to tell if they are significant. For example, in the number 8200, it is not clear if the zeroes are significant or not. The number of significant digits in 8200 is at least two, but could be three or four. To avoid uncertainty, use scientific notation to place significant zeroes behind a decimal point:
 - 8.200×10^3 has four significant digits
 - 8.20×10^3 has three significant digits
 - 8.2×10^3 has two significant digits

Significant Digits and Uncertainty Cont. 4

Significant Digits in Multiplication, Division, Trig. functions, etc.

- In a calculation involving multiplication, division, trigonometric functions, etc., the number of significant digits in an answer should equal the least number of significant digits in any one of the numbers being multiplied, divided etc.
- Thus in evaluating $\sin(kx)$, where $k = 0.097 \text{ m}^{-1}$ (two significant digits) and $x = 4.73 \text{ m}$ (three significant digits), the answer should have two significant digits.
- Note that whole numbers have essentially an unlimited number of significant digits. As an example, if a hair dryer uses 1.2 kW of power, then 2 identical hairdryers use 2.4 kW:
- $1.2 \text{ kW} \{2 \text{ sig. dig.}\} * 2 \{\text{unlimited sig. dig.}\} = 2.4 \text{ kW} \{2 \text{ sig. dig.}\}$

Significant Digits and Uncertainty Cont. 5

- Significant Digits in Addition and Subtraction
- When quantities are being added or subtracted, the number of decimal places in the answer should be the same as the least number of decimal places in any of the numbers being added or subtracted.
- Example:

$$5.67 + 1.1 + 0.9378 = 7.7$$

Significant Digits and Uncertainty Cont. 6

- Keep One Extra Digit in Intermediate Answers (round-off error)
- When doing multi-step calculations, keep at least one more significant digit in intermediate results than needed in your final answer.
- For instance, if a final answer requires two significant digits, then carry at least three significant digits in calculations. If you round-off all your intermediate answers to only two digits, you are discarding the information contained in the third digit, and as a result the second digit in your final answer might be incorrect. (This phenomenon is known as "round-off error.")

Significant Digits and Uncertainty Cont. 7

- Keep One Extra Digit in Intermediate Answers (round-off error)
- The Patriot missile defense system used during the Gulf War was rendered ineffective due to round off error[†]. The system used an integer timing register which was incremented at intervals of 0.1s. However, the integers were converted to decimal numbers by multiplying by the binary approximation of 0.1,
- As a result, after 100 hours (3.6×10^6 ticks), an error of ≈ 0.3433 seconds had accumulated. This discrepancy caused the Patriot system to continuously recycle itself instead of targeting properly.
- As a result, an Iraqi Scud missile could not be targeted and it detonated on a barracks, killing 28 people.

Significant Digits and Uncertainty Cont. 8

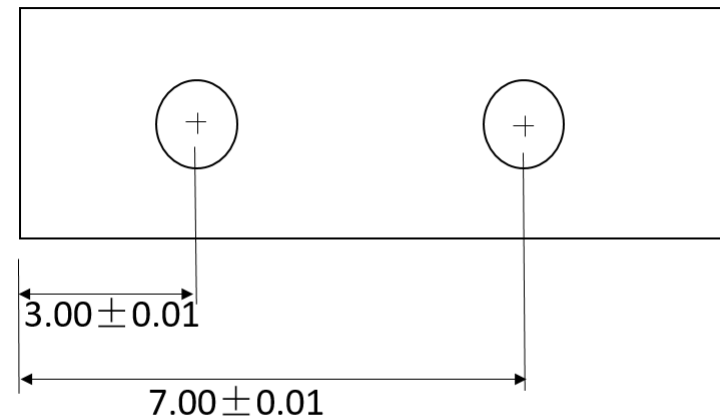
- The Two Greatest Sins Regarding Significant Digits
- Rounding Significant Digits and Uncertainty Cont. 8
- Rounding off to (for example) two digits in an intermediate answer, and then writing three digits in the final answer.
- Writing more digits in an answer (intermediate or final) than justified by the number of digits in the data.
- This latter “sin” is seen often in manufacturing settings, reporting measurements to more decimal places than available instruments could record. This does not inspire confidence in the ability of the employee reporting the data.

Significant Digits and Uncertainty Cont. 9

- Summary:
- When measuring, the number of digits, i.e. significant figures, reported for a numerical quantity conveys the quality of the measurement or analysis to the reader.
- When recording data or calculating numerical values, the precision of these values, which is represented by the number of digits, is vital information.
- Measuring instruments have their limits, just as your senses have their limits. One of your tasks, in addition to learning how to use various measuring instruments properly, will be to correctly determine the precision of the measuring devices that you use.

Real-world application: Tolerance Stacking

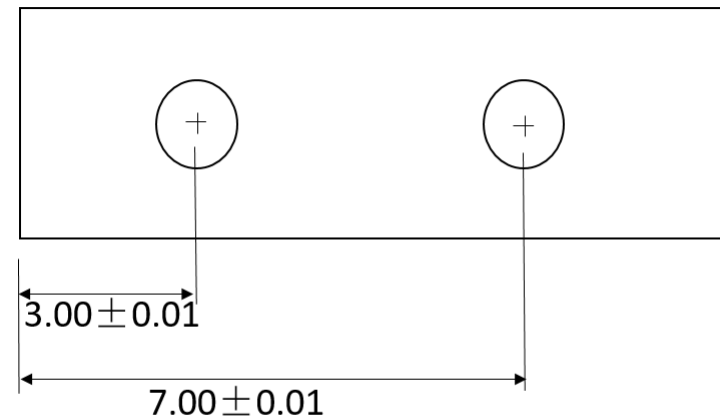
- Tolerance stack-ups are accumulations of variations on drawings or in part assemblies.
- Example:
- What is the effective
- dimension and
- tolerance between
- the two holes*?



*all measurements are in cm

Real-world application: Tolerance Stacking Cont.

- The furthest apart the two centers can be is
 - $7.01 - 2.99 = 4.02$
- The closest is
 - $6.99 - 3.01 = 3.98$
- Thus, the effective dimension and tolerance is 4.00 ± 0.02



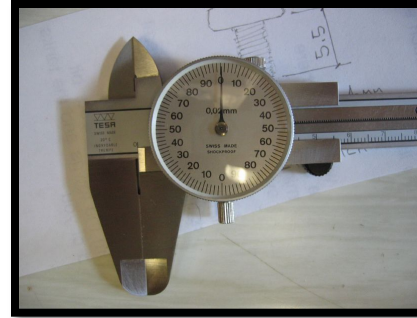
*all measurements are in cm

Our Goals for Precision Measurement -

- To become familiar with 3 basic measurement tools (ruler, calliper, and micrometer)
- Understand the range and tolerance for each tool
- Understand tool selection principle

We will focus on “DIMENSIONAL ANALYSIS”

- Calipers
 - Dial format
 - Digital format
- Micrometers (specialized caliper)



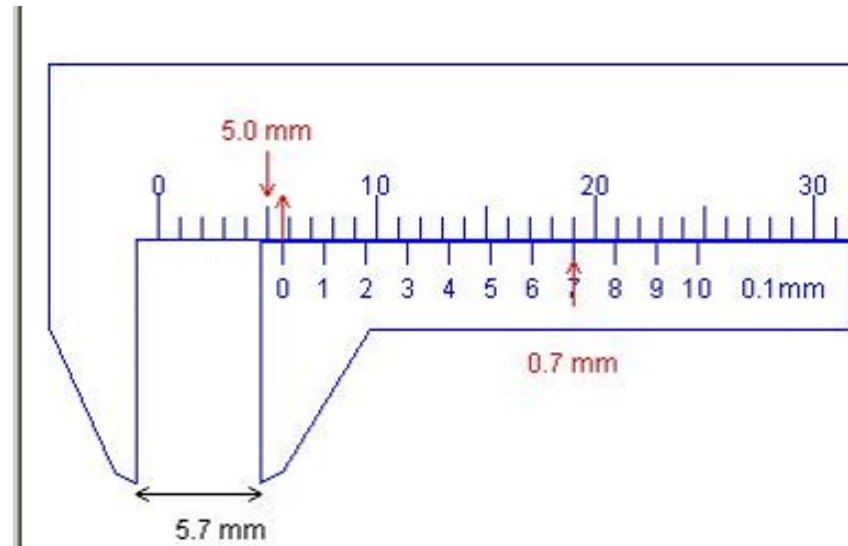
Calipers

- Used for
 - Outside dimensions
 - Inside dimensions
- Proper and clean contact of opposing surfaces with proper pressure is critical to accurate measurements
 - Correct: consistent, firm touch
 - Too much force: results in an under indication because part and tool distort
 - Too little force: gives insufficient contact and an over indication

Side note: Uncertainty with Vernier scale

- When using a Vernier scale, the level of precision depends on the difference between the size of the smallest division on the main scale and the largest measurement possible on the Vernier scale.
- Uncertainty with a Vernier scale =
 - Smallest measurement on the main scale- Largest measurement on the Vernier

Side note: Uncertainty with Vernier scale - caliper

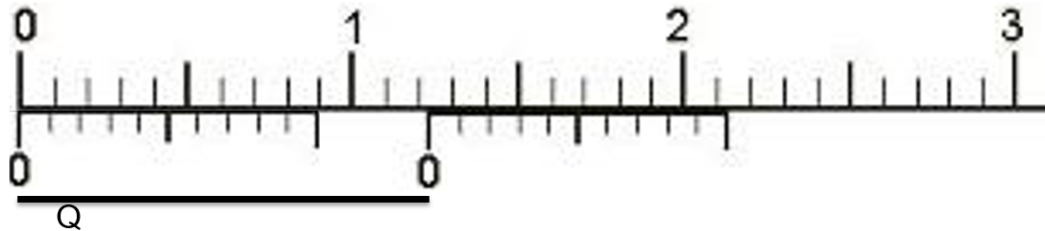


On this caliper:

- The zero is past the mark for 5.0mm but hasn't reached the 6.0mm mark
- The 7 on the Vernier scale best matches with a mark on the main scale
- Measurement: $5.7 \pm 0.1\text{mm}$

Side note: Uncertainty with Vernier scale - ruler

How long is line Q? Assume each number mark is a centimeter.



With the zero mark at the end of the line, the 0.03 mark lines up best with a mark on the ruler.

Main scale (1mm) - Vernier scale (0.9mm) = 0.1mm
The reading above is $1.2\text{cm} + 0.03\text{cm} = 1.23 \pm 0.01\text{cm}$

Micrometers

- Typical types
 - Outside micrometer (aka micrometer caliper), typically used to measure wires, spheres, shafts and blocks
 - Inside micrometer, used to measure the diameter of holes
 - Depth micrometer, measures depths of slots and steps
 - Bore micrometer, typically a three-anvil head on a micrometer base used to accurately measure inside diameters
 - Tube micrometer, used to measure the thickness of tubes
- Again, proper and clean contact of opposing surfaces with proper pressure is critical to accuracy

Outside Micrometer

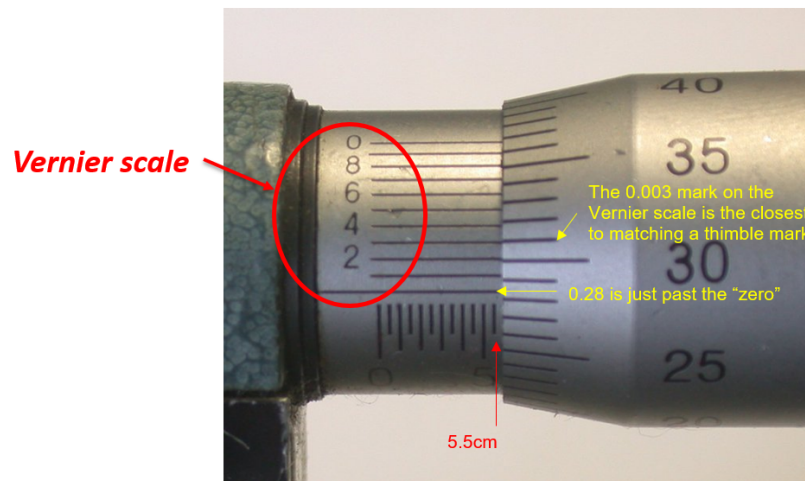
- Each full turn of spindle measures
 - 0.025" if using inch scale device (40 threads/inch)
 - 0.5 millimeter (mm) if using metric scale device



Unless otherwise marked, Most calipers and micrometers will have marked precision limits

Outside Micrometer Cont.

To get value of decimal place between smallest scale markings, use Vernier scale



5.783cm \pm 0.001cm measurement

Side note: Uncertainty with Vernier scale – outside micrometer

To determine uncertainty on a micrometer

- Determine smallest measure on main scale:
 - 0.01
- Determine largest measurement on Vernier scale:
 - 0.009
- Then subtract to determine uncertainty
 - Uncertainty = $.010 - .009 = .001$

Usage Notes

- Keep devices:
 - Calibrated
 - Clean
 - Safe (e.g. don't drop them)
- Be consistent in how you use devices
- Temperature will affect measurements !!!

Usage Notes Cont.

- Keep devices:
 - Calibrated – if not, this affects the uncertainty of your reading.
 - For example: if your micrometer does not close on zero, the “zero point” reading is added to the measurement reading along with the uncertainty.

Understand Equipment Tolerance and Selection Principle

Practice dimensional analysis :

- Measure the OD (outside dimension) of three nuts using a ruler, a caliper and a micrometer
 - Measure the T (thickness) of the smallest and largest nuts using a micrometer
 - Measure the ID (inside dimension) of the largest nut using a caliper
- ** Perform all measurements 3 times, and record result on worksheet provided (apply GDP)**