Pharmaceutical measurement

Objectives

- Describe instruments for volumetric measurement and characterize their differences in application and accuracy.
- Describe the correct procedure when using a pharmaceutical balance.
- Define *sensitivity requirement* and apply it in calculations.
- Perform calculations by the aliquot method.
- Demonstrate an understanding of *percentage of error* in pharmaceutical measurement.

MEASUREMENT OF VOLUME

- Common instruments for the pharmaceutical measurement of volume range from **micropipets** and **burettes** used in analytic procedures to large, industrial-size calibrated **vessels**.
- The selection of measuring instrument should be based on the level of precision required.

- In pharmacy practice, the **most common instruments for measuring volume** are **cylindric** and **conical (cone-shaped)** graduates (***Fig. 3.1***).
- For the measurement of small volumes, the pharmacist often uses a **calibrated syringe** or, when required, a **pipette**.
- **cylindric graduates** are calibrated in **metric units**,
- **conical graduates** are usually **dual-scale**, i.e., calibrated in both metric and apothecary units of volume.

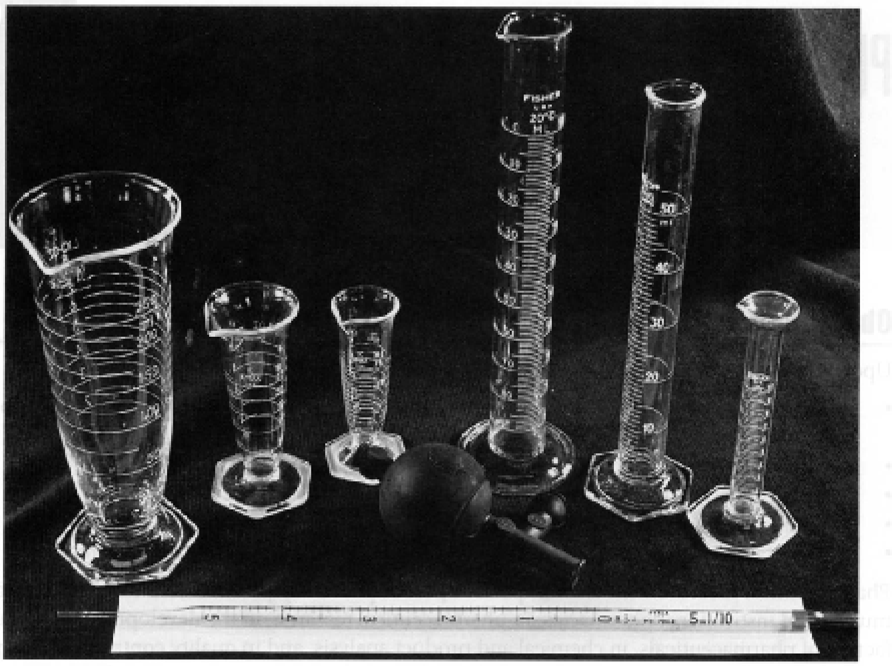

FIGURE 3.1 Examples of conical and cylindric graduates, a pipet, and a pipet-filling bulb for volumetric measurement.

- [NOTE: metric units of volume are described in Chapter 2 and Apothecaries' units are described in Appendix A.}
- Both glass and plastic graduates are commercially available in a number of capacities, ranging from 5 to 1000 milliliters and greater.

- As a general rule, it is best to select the graduate with a capacity equal to or just exceeding the volume to be measured.
- Measurement of small volumes in large graduates tends to increase the size of the error.
- The design of a volumetric apparatus is an important factor in measurement accuracy; the narrower the bore or chamber, the lesser the error in reading the meniscus and the more accurate the measurement (Fig. 3.2).

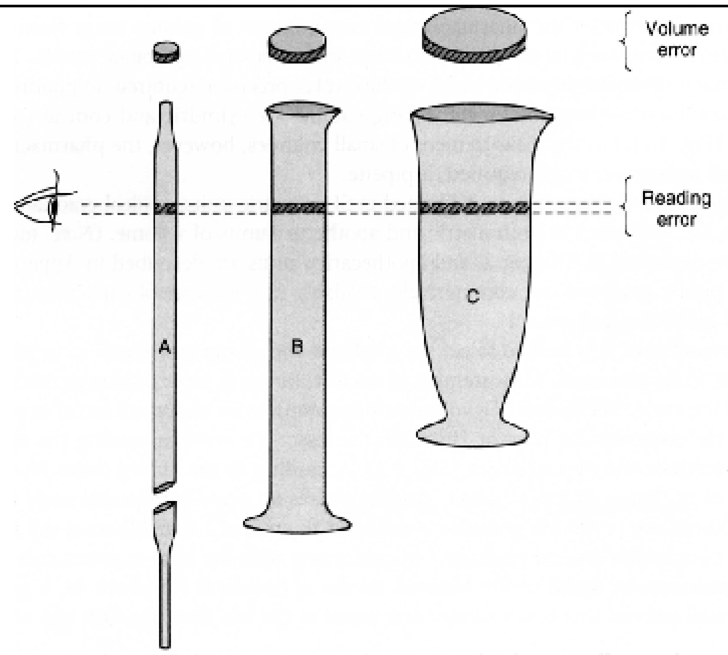

FIGURE 3.2 Volume error differentials due to instrument diameters. **(A)**, volumetric pipet; **(B)**, cylindric graduate; and **(C)**, conical graduate.

- According to the United States Pharmacopeia"
  - a deviation of ± 1 mm in the meniscus (圓筒內液體的凹凸面) reading causes an error of approximately
    - **0.5 milliliter** when a 100-milliliter **cylindric graduate**
    - **1.8 milliliter** at the 100-milliliter mark in a comparable **conical graduate**.

- In conformity with the legal requirements for **pharmaceutical graduates**, as stated in the National Bureau of Standards Handbook 44, a **graduate** shall have an **initial interval that is not subdivided**, equal to **not less than one-fifth** and **not more than one-fourth** of the **capacity of the graduate**.
- **Conical graduates** of less that **25-milliliter** capacities are not recommended for use in pharmaceutical compounding.

MEASUREMENT OF WEIGHT

- The selection of implements:
  1. **balances**, and **scales** for pharmaceutical measurement depends on the task at hand,
  2. **highly sensitive electronic analytic balances** in **performing assay tests**
  3. **prescription balances** in extemporaneous compounding procedures
  4. **large capacity scales** in the industrial manufacturing and production of pharmaceutical agents.
- Each instrument used must meet **established standards for sensitivity, accuracy, and capacity**.

- **Class A prescription balances** (Fig. 3.3) are designed for the **weighing of medicinal** or other substances required in the filling of prescriptions or in **small-scale compounding**.
- Some prescription balances have a **weighbeam** and **rider**, and others a dial, to add up to 1 gram of weight.
  - Additional external weights may be added to the **right- hand balance pan**.
  - The material to be weighed is placed on the **left-hand** pan.

FIGURE 3.3 Torbal torsion balance and Ohaus electronic balance. *(Courtesy of Total Pharmacy Supply, Inc.)*

- **Powder papers** are added to each pan before any additions
- the balance is leveled by **leveling feet** or **balancing screws**.
- Weighings are performed through the careful **portion-wise (by spatula**) addition and removal of the material being weighed, with the balance being arrested (**pans locked in place by the control knob**) during each addition and removal of material, and unarrested with the lid closed for determinations of balance rest points.

- When the unarrested pans neither ascend nor descend and the index plate shows the needle is in the center, the material and balance weights are considered **equivalent**.
- The student may wish to refer to other sources, such as the **United States Pharmacopeia**, for more detailed information on the proper use and testing of the prescription balance.

Class A prescription balance

- should be used in all prescription compounding procedures.
- have a sensitivity requirement (SR) of 6 milligrams or less with no load and with a load of 10 grams in each pan.
- To avoid errors of greater than 5% when using this balance, the pharmacist should not weigh less than 120 milligrams of material (i.e., a 5% error in a weighing of 120 milligrams = 6 milligrams).
- Most commercially available Class A balances have a **maximum capacity of 120 grams**.

Sensitivity requirement

- is defined as the load that will cause a change of one division on the index plate of the balance.
- may be determined by the following procedure:
  1. Level the balance.
  2. Determine the rest point of the balance.
  3. Determine the smallest weight that causes the rest point to shift one division on the index plate.

- many pharmacies utilize **high precision electronic analytical balances** to weigh very small quantities (Fig. 3.4).
  - are capable of weighing accurately 0.1 milligram,
  - are self-calibrating,
  - are equipped with convenient digital readout features.
  - The usual maximum capacities: 60 grams to 210 grams depending upon the model.
- A set of metric weights that may be used to weigh materials on a prescription balance and/or used to calibrate an analytical balance is shown in Figure 3.5.

FIGURE 3.4 Sartorious BasicLite analytical balance. *(Courtesy of Sartorius Corporation.)*

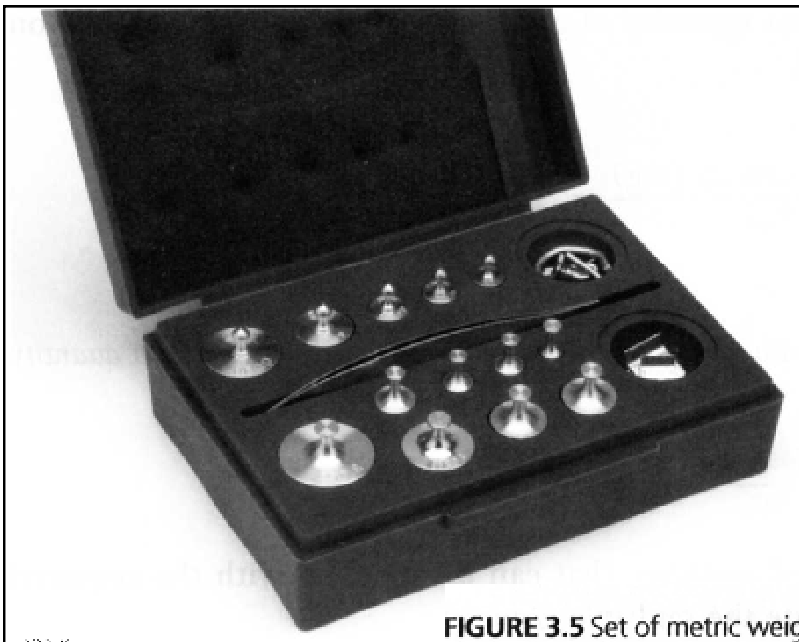

FIGURE 3.5 Set of metric weights. (Courtesy of Mettler-Toledo, Inc.)

ALIQUOT METHOD OF WEIGHING AND MEASURING

- When a **degree of precision** in measurement that is **beyond the capacity of the instrument** at hand is required, the pharmacist may achieve the desired precision by calculating and measuring in terms of **aliquot parts (能整除部份).**

Weighing by the Aliquot Method

- small quantities of a substance may be obtained within the desired degree of accuracy by
  - weighing a **larger-than-needed portion** of the substance,
  - **diluting** it with an **inert material**,
  - **weighing a portion (aliquot) of the mixture** calculated to **contain the desired amount** of the needed substance.

Weighing by the Aliquot Method

- A step-wise description of the procedure is depicted in Figure 3.6 :
  - ***Preliminary Step*. Calculate the smallest quantity of a substance that can be weighed on the balance with the desired precision**.
  - *Example: on a balance with a SR of 6 mg, and with an acceptable error of no greater than 5% , a quantity of not less than 120 mg must be weighed*.

Preliminary Step. **Calculate the smallest quantity of a substance that can be weighed on the balance with the desired precision.**

The equation used:

$$\frac{100\% \times \text{Sensitivity Requirement (mg)}}{\text{Acceptable Error (\%)}} = \text{Smallest Quantity (mg)}$$

Example:

On a balance with an SR of 6 mg, and with an acceptable error of no greater than 5%, a quantity of not less than 120 mg must be weighed.

$$\left[\frac{100\% \times 6\text{ mg}}{5\%} = 120\text{ mg}\right]$$

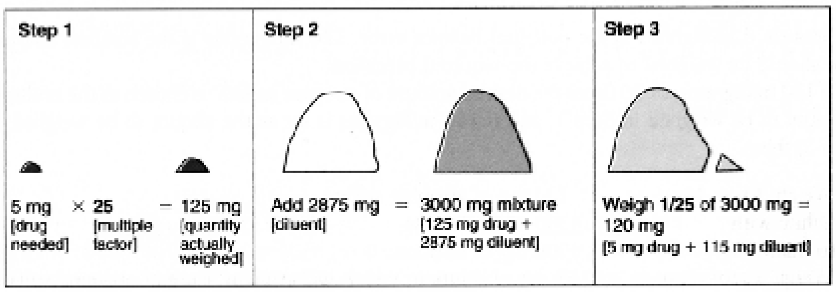

FIGURE 3.6 Depiction of the aliquot method of weighing using the example described on the next page.

Step 1. Select a multiple of the desired quantity that can be weighed with the required precision.

- If the quantity of a required substance is *less than* the minimum weighable amount, select a "multiple" of the required quantity that will yield an amount equal to or greater than the minimum weighable amount. (A larger-than-necessary multiple may be used to exceed the minimum accuracy desired.)
- *Example:*
  If the balance in the example in the preliminary step is used, and if 5 mg of a drug substance is required on a prescription, then a quantity at least **25 times** *(the multiple) the desired amount, or 125 mg (5 mg × 25), must be weighed for the desired accuracy.* (If a larger multiple is used, say 30, and 150 mg of the substance is weighed (5 mg × 30), then a weighing error of only 4% would result.)

Step 1. Select a multiple of the desired quantity that can be weighed with the required precision.

- If the quantity of a required substance is *less than* the minimum weighable amount, select a "**multiple**" of the required quantity that will yield an amount **equal to or greater than the minimum weighable amount**. [A **larger-than-necessary multiple may be used to exceed the minimum accuracy desired**.}

Step 1. Select a multiple of the desired quantity that can be weighed with the required precision.

- *Example: if the balance in the example in the preliminary step is used and if 5 mg of a drug substance is required on a prescription, then a quantity at least* ***25 times*** *{the "multiple") the desired amount, or 125 mg (5 mg X 25), must be weighed for the desired accuracy*.
- (If a larger multiple is used, say 30, and 150 mg of the substance is weighed [5 mg X 30}, then a weighing error of only 4% would result.)

Step 2. Dilute the multiple quantity with an inert substance.

- The ***amount of inert diluent*** to use is determined by the fact that the **aliquot portion of the drug-diluent mixture weighed in *Step 3*** must be equal to or greater than the minimum weighable quantity previously determined.
- By **multiplying the amount of the aliquot portion to weigh in Step 3 by the multiple selected in Step 1**, the **total quantity of the mixture to prepare is determined**.

Step 2. Dilute the multiple quantity with an inert substance.

- *Example: according to the preliminary step, 120 milligrams or more must be weighed for the desired accuracy.*
- *If we decide on 120 mg for the aliquot portion in Step 3, and multiply it by the multiple selected in Step 1 (i.e., 25), we arrive at 3,000 mg for the total quantity of the drug-diluent mixture to prepare.*
- *Subtracting the 125 mg of drug weighed in Step 1, we must add 2,875 mg of diluent to prepare the 3,000 mg of drug-diluent mixture.*

Step 3. **Weigh the aliquot portion of the dilution that contains the desired quantity.**

- Since **25 *times*** the needed amount of drug substance was weighed (*Step 1*), an aliquot part equal to **1/25** of the 3000-mg drug-diluent mixture, or 120 mg, will contain the required quantity of drug substance.
- *Proof:* 1/25 × 125 mg (drug substance weighed in *Step 1*) = 5 mg
  1/25 × 2875 mg (diluent weighed in *Step 2*) = <u>115 mg</u>
  120 mg aliquot part

- *Example: a torsion prescription balance has a sensitivity requirement of 6 milligrams. Explain how you would weigh 4 milligrams of atropine sulfate with an accuracy of ± 5%, using lactose as the diluent*.
  - ∵ 6 milligrams is the potential balance error, 120 milligrams is the smallest amount that should be weighed to achieve the required precision.
  - If 120 milligrams, or 30 times the desired amount of atropine sulfate, is chosen as the multiple quantity to be weighed in Step 1,
  - if 150 milligrams is set as the aliquot to be weighed in Step 3, then:
    1. Weigh 30 X 4 mg, or 120 mg of atropine sulfate
    2. Dilute with 4380 mg of lactose
       to make 4500 (150*30) mg of dilution
    3. Weigh 1/30 of dilution, or 150 mg of dilution, which will contain 4 mg of atropine sulfate, answer.

$$proof: \quad \frac{4500\,mg\,(diluent)}{150\,mg\,(diluent)} = \frac{120\,mg\,(atropine\,sulfate)}{x\,mg\,(atropine\,sulfate)}$$

$$= 4\,mg, answer.$$

- In this example, the weight of the aliquot was arbitrarily set as 150 mg, which exceeds the weight of the multiple quantity, as it preferably should.
- If 120 mg had been set as the aliquot, the multiple quantity should have been diluted with 3,480 mg of lactose to get 3,600 mg of dilution, and the aliquot of 120 mg, would have contained 4 mg of atropine sulfate.
- if 200 mg had been set as the aliquot, the multiple quantity of atropine sulfate should have been diluted with 5,880 mg of lactose to get 6,000 mg of dilution.

A torsion prescription balance has a sensitivity requirement of 6.5 milligrams. Explain how you would weigh 15 milligrams of atropine sulfate with an accuracy of ± 5%, using lactose as the diluent.

- Because 6.5 milligrams is the potential balance error, 130 milligrams (20 X 6.5 milligrams) is the smallest amount that should be weighed to achieve the required accuracy.
- If 10 is chosen as the multiple, and if 130 milligrams is set as the weight of the aliquot, then:
  1. Weigh 10 X 15 mg or 150 mg of atropine sulfate
  2. Dilute with 1150 mg of lactose
     to make 1300 mg of dilution
  3. Weigh 1/10 of dilution, or 130 mg, which will contain 15 mg of atropine sulfate, answer.

Measuring Volume by the aliquot Method

- may be used when relatively small volumes must be measured with great precision:
  - Step 1. Select a multiple of the desired quantity that can be measured with the required precision.
  - Step 2. Dilute the multiple quantity with a compatible diluent (usually a solvent for the liquid to be measured) to an amount evenly divisible by the multiple selected.
  - Step 3. Measure the aliquot of the dilution that contains the quantity originally desired.

A prescription calls for 0.5 milliliter of hydrochloric acid. Using a 10-milliliter graduate calibrated from 2 to 10 milliliters in 1 -milliliter divisions, explain how you would obtain the desired quantity of hydrochloric acid by the aliquot method.

- If 4 is chosen as the multiple, and if 2 milliliters (mL) is set as the volume of the aliquot, then:
  1. Measure 4 X 0.5 mL, or 2 mL of the acid
  2. Dilute with 6 mL of water
  3. to make 8 mL of dilution
  4. Measure 1/4 of dilution, or 2 mL of dilution, which will contain 0.5 mL of hydrochloric acid, answer.

A prescription calls for 0.2 mL of clove oil. Using a 5-mL graduate calibrated in units of'0.5 mL, how would you obtain the required amount of clove oil using the aliquot method and alcohol as the diluent?

- If 5 is chosen as the multiple, then:
  1. Measure 5 X 0.2 mL, or 1.0 mL of clove oil
  2. Dilute with 4.0 mL of alcohol
  3. to make 5.0 mL of dilution
  4. Measure 1/5 of the dilution, or 1.0 mL, which contains 0.2 mL of clove oil, answer.

LEAST WEIGHABLE QUANTITY METHOD OF WEIGHING

- may be used as an alternative to the aliquot method of weighing to obtain small quantities of a drug substance.
- After determining the quantity of drug substance that is desired and the smallest quantity that can be weighed on the balance with the desired degree of accuracy, the procedure is as follows:
  - Step 1. Weigh an amount of the drug substance that is equal to or greater than the least weighable quantity.
  - Step 2. Dilute the drug substance with a calculated quantity of inert diluent such that a predetermined quantity of the drug-diluent mixture will contain the desired quantity of drug.

If 20 milligrams of a drug substance are needed to fill a prescription, explain how you would obtain this amount of drug with an accuracy of ± 5% using a balance with a sensitivity requirement of 6 milligrams. Use lactose as the diluent.

- 20 milligrams is the amount of drug substance needed.
- The least weighable quantity would be 120 milligrams.
- The amount of drug substance to be weighed, therefore, must be equal to or greater than 120 milligrams. 120 milligrams of drug substance is weighed.
- In calculating the amount of diluent to use, a predetermined quantity of drug-diluent mixture must be selected to contain the desired 20 milligrams of drug substance.
- The quantity selected must be greater than 120 milligrams because the drug-diluent mixture must be obtained accurately through weighing on the balance. An amount of 150 milligrams may be arbitrarily selected.
- The total amount of diluent to use may then be determined through the calculation of the following proportion:

$$\frac{20\,mg\ (\text{drug needed for R})}{150\,mg\ (\text{drug} - \text{diluent mix. to use in R})} = \frac{120\,mg\ (\text{total drug substance weight})}{x\,mg\ (\text{total amount of drug} - \text{diluent mix. prepared})}$$

x = 900 milligrams (mg) of the drug-diluent mixture to prepare

Hence, 900 mg — 120 mg = 780 mg of diluent (lactose) to use, answer.

•each weighing, including that of the drug substance, the diluent, and the drug-diluent mixture, must be determined to be equal to or greater than the least weighable quantity as determined for the balance used and accuracy desired.

CALCULATIONS CAPSULE

Weighing Accuracy

- The sensitivity requirement (SR) of a balance must be known or determined. An SR of 6 mg is usual.
- An error in weighing of ± 5% or less is acceptable.
- The smallest quantity that should be weighed on a prescription balance is determined by the equation:

$$\frac{100\% \times \text{Sensitivity Requirement (mg)}}{\text{Acceptable Error (\%)}} = \text{Smallest Quantity (mg)}$$

That quantity is usually about 120 mg.

- To weigh smaller quantities, an electronic balance or the aliquot method of weighing should be used.

PERCENTAGE OF ERROR

- Because measurements are never absolutely accurate, it is important for the pharmacist to recognize the limitations of the instruments used and the magnitude of the errors that may be incurred.
- When a pharmacist measures a volume of liquid or weighs a material, two quantities become important:
  1. the apparent weight or volume measured,
  2. the possible excess or deficiency in the actual quantity obtained.

- Percentage of error may be defined as the **maximum potential error** multiplied by 100 and divided by the quantity desired.
- The calculation may be formulated as follows:

$$\frac{Error \times 100\%}{Quantity\ desired} = Percentage\ of\ error$$

Calculating Percentage Error in Volumetric Measurement

- The precision obtained in a given measurement depends on:
  - the selection of the measuring device used (e.g., pipet, graduated cylinder),
  - the volume of liquid being measured,
  - the skill and care of the pharmacist.
- The **percentage error in a measurement of volume** may be calculated from the *preceding formula*, relating the **volume in error** (determined through devices of greater precision) to the **volume desired** (or apparently measured).

- Example: *Using a graduated cylinder, a pharmacist measured 30 milliliters of a liquid. On subsequent examination, using a narrow-gauge burette, it was determined that the pharmacist had actually measured 32 milliliters. What was the* ***percentage of error*** *in the original measurement*?
  - 32 milliliters - 30 milliliters = 2 milliliters, the volume of error

$$\frac{2\ mL \times 100\%}{30\ mL} = 6.7\%,\ answer.$$

Calculating Percentage Error in Weighing

- The **various scales and balances** used in pharmaceutical weighing have ascribed to them **different degrees of precision**.
- The **sensitivity of a balance** may be defined in several ways.
- **Balance manufacturers** use the term to designate the **smallest weight** that will cause a perceptible movement of the balance, shown by the **balance's indicator scale**.

Calculating Percentage Error in Weighing

- **Prescription balances** have established **standards of precision** based on a **Sensitivity Requirement (SR),** defined by the **United States Pharmacopeia** as "the maximum change in load that will cause a specified change, **one subdivision on the index plate**, in the position of rest of the indicating element or elements of the balance.

Calculating Percentage Error in Weighing

- "**Class A" prescription balances**, generally utilized in pharmacies, have a **SR** (or **maximum potential error**) of **6 milligrams** or less.
  - ***The smaller the weight required to move the indicating element, the more sensitive the balance***.

- Examples: *When the maximum potential error is ± 4 milligrams in a total of 100 milligrams, what is the percentage of error*?

$$\frac{4 \times 100\%}{100} = 4\%, answer.$$

A prescription calls for 800 milligrams of a substance. After weighing this amount on a balance, the pharmacist decides to check by weighing it again on a more sensitive balance, which registers only 750 milligrams. Because the first weighing was 50 milligrams short of the desired amount, what was the percentage of error?

$$\frac{50\times 100\%}{800}=6.25\%, \mathit{answer}.$$

- If a certain percentage of error is not to be exceeded, and the maximum potential error of an instrument is known, it is possible to calculate the smallest quantity that can be measured within the desired accuracy.
- A convenient formula follows:

$$\frac{100\times \mathit{Maximum\ potential\ error}}{\mathit{Permissible\ percentage\ of\ error}}=\mathit{Smallest\ quantity}$$

Example; *What is the smallest quantity that can be weighed with a potential error of not more than 5% on a balance sensitive to 6 milligrams*?

$$\frac{100\times 6\,mg}{5}=120\,mg, \mathit{answer}.$$

CASE IN POINT 3.1: A pharmacist is asked to compound the following formula for the preparation of 100 capsules:[3]

Estriol	200 mg
Estrone	25 mg
Estradiol	25 mg
Methocel E4M	10 g
Lactose	23.75 g

Using a balance that has an SR of 6 mg, the aliquot method of weighing, lactose as the diluent, and an error in weighing of 4%, show, by calculations, how the correct quantity of estrone can be obtained to accurately compound the formula.

CASE IN POINT 3.2: A physician prescribed 25 4-mg capsules of a drug for a special needs patient, knowing that the dose prescribed was considered "subtherapeutic." The lowest strength commercially available tablets contain 25 mg.

The pharmacist decided to select the minimum required number of 25-mg tablets (4 tablets); reduce them to a powder with a mortar and pestle; weigh the powder (280 mg); and continue the process using the aliquot method. She called upon her pharmacy student intern to calculate (a) the minimum quantity of lactose (diluent) to use in preparing the crushed tablet-diluent mixture and (b) the quantity of the mixture to use to fill each capsule.

The prescription balance had a SR of 6 mg and a weighing error of 5% was acceptable. Show your calculations for (a) and (b), and (c) prove that your answer to (b) is correct by demonstrating that each capsule would indeed contain 4 mg of drug.