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This article reviews engineering methods for scale specifications and theory of calibration requirements in reference to weighing processes procedures, operation methods, and standards for scales tolerances.

## Specification and Calibration Requirements for Industrial Scales in Pharmaceutical Applications

by Yefim S. Gudesblat, PE

### Introduction

Performance and accuracy of industrial scales in pharmaceutical applications are covered by current Good Manufacturing Practices (cGMPs). Verification of proper operation of process scales is an important factor in finished product Quality Assurance (QA) programs. Incorrect weighing, additions of materials and components in validated processes of formulation, dispensing, and mixing are most likely not recoverable and costly to businesses. Mistakenly released products within an established QA program could be detrimental to patients' health and manufacturers' reputation including legal implications.

This article presents standardized classification of accuracies for weighing systems and describes specifications, methodologies, calibration procedures, routines, and related metrology theories in reference to the current standard. Calibration checks and certification methods are reviewed for illustrations of importance in preservation of weighing integrity.

The Product Master Formula and Batch Records contain information concerning weighing specifications for additions of chemical components. Weighing specifications are scientifically developed to control critical parameters related to scale functional activities. Production recipes include sequential order of chemical component additions, maximum and minimum amounts for each chemical component, mixing time, and feeding rates.

Weighing additions of chemical components will naturally fluctuate from batch to batch. Therefore, cGMPs require that Standard Oper-

ating Procedures (SOP) for weighing processes will cover maximum allowed deviations for weights in the process formulas. Products made outside of defined weighing specifications will oblige sanctions of product quarantine for investigation. The almost certain outcome from investigations will lead to destruction or rework of manufactured material.

Permitted variations in component weights need to agree with the scale capabilities. Qualification tests and procedures for scales in validated processes will provide the necessary assurance of accurate weighing execution. Verification of the scale's compliance to the process requirements is an important phase for the system qualification and validation. Selections of calibration procedures, calibration frequencies, and certification methods for weighing systems depend on application, accuracies, and possibilities for in-time accuracy changes.

The manufacturing processes in weighing applications are limited by the scale's calibration accuracy. Scale accuracies are established by scale classes. The product quality compliance requires certification of scales traceable to National Institute of Standards and Technology (NIST) Weighing Standards. Calibration procedures deal with formats of recorded data to establish documentation layout and flow designed to assure traceability of collected data.

Performance verification of weighing measuring devices consists of two parts. One is a calibration certification and the other is a calibration check. The calibration certification summarizes a methodical process defined by a written and approved procedure developed for a

range of measurements. A calibration check is a simplified confirmation of the scale performance. Usually calibration checks are represented by one or two test measurements.

Properly established scale tolerances, calibration procedures, and scale functional tests are very important issues for QA programs and production costs. CGMP and metrology requirements issues related to scale capabilities, weighing tolerances, and calibration methodology are addressed in this paper.

The governing document for technical requirements of weighing and measuring devices is Handbook 44. Handbook 44 is the current standard published by NIST for all industrial scales and utilized in engineering practices for determination of weighing tolerances and calibration limits. Handbook 44 was adapted by the 84th National Conference on Weights and Measurements in 1999.

### Weighing Process Limits and Scale Tolerances

Weighing requirements for manufacturing processes are represented by upper and lower limits of weight for materials added and mixed at established time intervals. Each process step is intended to be repeatable from batch to batch and executable in accordance with validated formulas.

One of the process characteristics could be defined by the capability of the acceptable fluctuations in weighing additions. Qualified weighing equipment dedicated to the validated processes could be characterized by tolerances and calibration limits of measurements. Capabilities of scales for employed processes represented by tolerances and calibration limits cannot exceed process capabilities characterized by allowable fluctuation in weighing additions.

Aside from possible mistakes initiated by incorrect weighing techniques and applications, there are recognized errors in the actual data produced by any instrument. The instrument inaccuracies are originated from round-off errors as a result of utilizing displays with limited numbers of digits and truncation errors originated from finite approximation of limiting processes. Actual measurements finalized by any instrument display or printout must be rounded-off to the number of decimal places justified by the application.

Understanding the mathematical definition for significant digits is very important in metrology and basic principles of

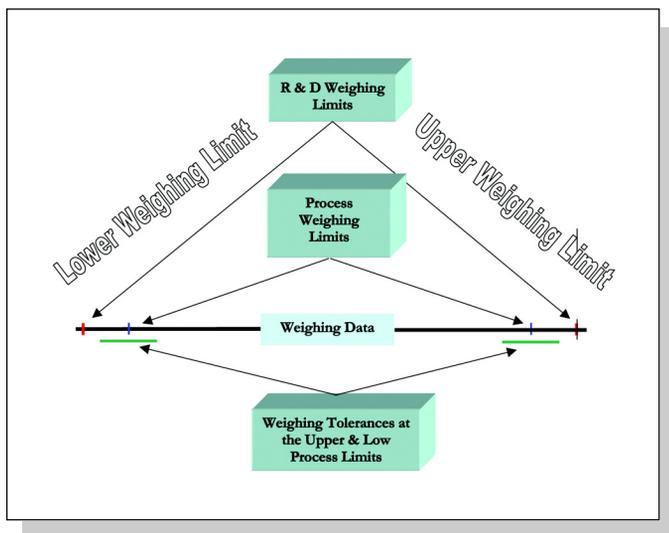


Figure 1. Weighing system tolerance and process limits.

data interpretations. The significant digits in a displayed or printed number included the left-most non-zero digits to right-most digits registered. The established number of significant digits in produced data characterizes accuracy of that data. Table A explains the purpose of significant digits.

Pharmaceutical weighing processes (as well as any weighing processes) are subject to a defined range of chemical additions. For example, the Master Formula of a pharmaceutical process requires an addition of a chemical X. The addition of chemical X is outlined as a minimum amount of 1200.0 Kg and maximum of 1210.0 Kg; which means that the added weight of 1205.7 Kg will be allowable, but 1210.1 Kg or 1199.9 Kg will not be acceptable.

Typically, limits are established by R&D after the process scale-up for production. Limits are presented in a format of an essential significant digit i.e., 1200.0 Kg and 1200 Kg are different values because 1200.0 Kg represent possible measurements between 1199.95 Kg and 1200.04 Kg and 1200 Kg correspond to variation of measurements within 1199.5 Kg and 1200.4 Kg.

In our example, we like to identify the process scale as Class III with the display resolution of 0.5 Kg and consequent accuracy of  $\pm 1$  Kg. The preset process limits (1200 Kg to 1210 Kg) and the scale accuracy are not in conflict with process measurements. Compatibility of scales and requirements for weighing processes are very important for consistency and quality of the final pharmaceutical products. Below is a demonstration that proves this scale will be acceptable for the process.

The manufacturing procedure for the described chemical X addition identifies the target weight as  $1205 \pm 3.5$  Kg. From simple arithmetical calculations, the upper limit of measured weight documented in the manufacturing SOP is 1208.5 Kg and the low limit – 1201.5 Kg. The SOP limits are narrower than actual limits of 1200 Kg and 1210 Kg from R&D findings. The upper and lower weighing limits identified in the SOP are derived from the following calculations:

#### (a) Upper Limit

For a properly operated scale the registered weight of 1208.5 Kg (SOP upper limit =  $1205 + 3.5$  Kg) could be effectively 1209.9 Kg. The accuracy 1 Kg and display resolution of 0.5 Kg need to be considered in the actual measurements.

The scale display changes in increments of 0.5 Kg. Therefore, scale display may not change before weight change is above 0.4 Kg. The scale accuracy is identified as  $\pm 1$  Kg, and for the upper weight, 1 Kg and 0.4 Kg should be added to the displayed weight representing 1208.5 Kg.

#### (b) Lower Limit

For a properly functional scale, the registered weight of 1201.5 Kg (SOP upper limit =  $1205 - 3.5$  Kg) could be effectively 1200.1 Kg. The same accuracy 1 Kg and display resolution of 0.5 Kg needs to be considered in the actual measurements of the low limit.

The scale display changes in increments of 0.5 Kg. Therefore, the scale display may not change if the weight change is above 0.4 Kg. The scale accuracy is identified as  $\pm 1$  Kg, and for the lower weight, 1 Kg and 0.4 Kg should be subtracted from the displayed weight representing 1201.5 Kg.

Let's assume that a replacement scale is considered for the chemical X addition. A new scale system is specified for display of 1-Kg resolution, and therefore, accuracy ( $\pm 2$  Kg). The SOP

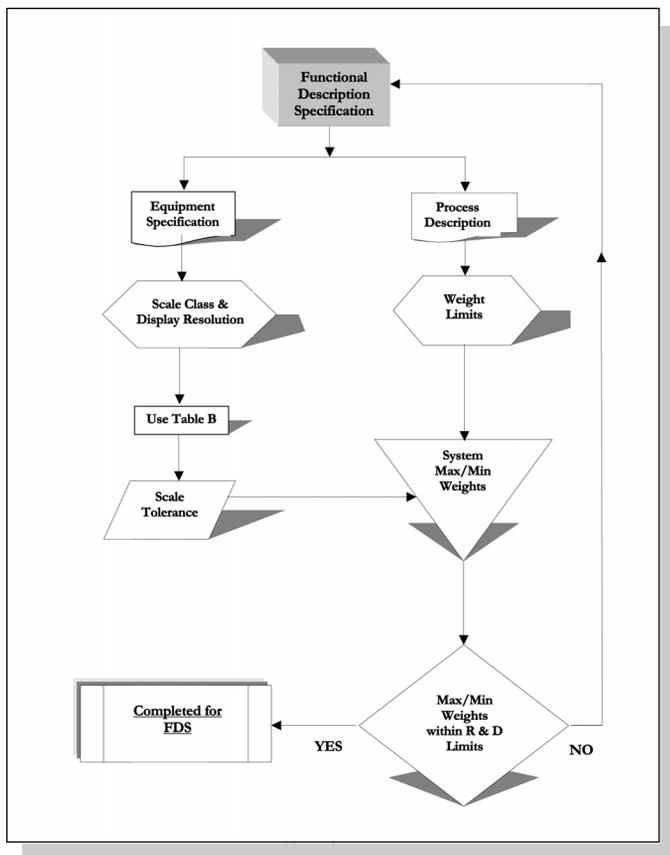


Figure 2. Coordination of weighing system tolerances and calibration limits.

limits for the new scale will require a change to  $1205 \pm 1$  Kg. This change is necessitated by the R&D established limits (1200.0 Kg and 1210.0 Kg) and the new scale specifications.

The replacement scale's upper process limit is 1206 Kg, which effectively can represent 1209.9 Kg. The effective weight of the upper limit considers  $\pm 2$  Kg scale tolerances and 1 Kg display resolution. The lower process weight limit of 1204 Kg may effectively be 1200.1 Kg. Calculations are the same as previously discussed.

Maintaining the weight additions with an accuracy of  $\pm 1$  Kg may not be practical, and therefore, this scale shall not be considered for the process. We cannot increase weight tolerances without exceeding the established R&D limits. Changing the process accuracy to  $\pm 2$  Kg may take weights outside of the R&D limits.

At  $\pm 2$ -Kg process accuracy, the displayed weight of 1203 Kg effectively could be below 1200.0 Kg. The scale tolerance  $\pm 3$  Kg and resolution of 1 Kg may be representative of 1299.1 Kg. The upper limit of 1207 Kg effectively could correspond to 1200.9 Kg. All calculations are implied from the same algorithm.

The above examples are presented to demonstrate the importance of scale selection for specific processes. The summarized procedure for verification of scales compatibility to the process is shown in Figure 1 and outlined below:

1. Retrieve the R&D limits for weighing application.
2. Verify scale tolerances and display resolution.
3. Check SOP (or new process requirements) for weighing setpoints and limits.
4. Add to the upper weighing limit identified in the SOP the scale tolerance in the represented resolution. The result will represent a possible (effective) weight on the scale at

the upper limit.

5. The same procedure can be applied in reverse to the lower weight limit. Subtract from the lowest weight permitted by the SOP the scale tolerance in the represented resolution. The result will represent a possible (effective) weight on the scale at the lower limit.
6. Compare the numbers in steps 4 and 5 to the R&D weighing limits. The upper and lower effective weights cannot exceed the R&D limits.

The weighing process tolerances at upper or lower process limits cannot extend further than R&D weighing limits in the product development protocol. Process operation limits must be set at sufficient levels in relation to weighing process tolerances and R&D limits. Properly established weighing process limits will assure quality, repeatability, and consistency of bulk formulation and compounding processes.

The process operation weighing limits after qualification and validation approvals could be found in a plant SOP for manufacturing sections. Calibration limits will be documented in the SOP for weighing systems calibration. Production and calibration personnel are obliged to comply with the approved SOPs. Properly established limits in the approved SOPs will assure repeatability of the processes and quality of finished product.

The weighing process tolerances, scale classes representing accuracy and sensitivity, and scale display resolution are interrelated. In the following sections of this article, methods and standards by which scale tolerances and weighing capabilities are determined will be discussed.

### Determine Weighing Process Tolerances

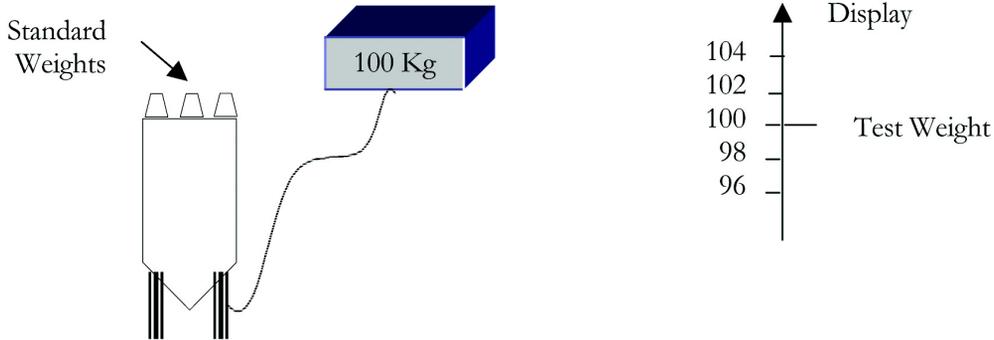
Performance and accuracies of weighing systems are governed by Handbook 44. Scale tolerances are defined by scale classes and range of measurements. Accuracies for calibration procedures are dictated by established tolerances. The methods described below represent minimum requirements that each scale must confirm.

Scale accuracies and calibration tolerances are interconnected. Calibration tolerances for all industrial scales can be established from data presented – Table B.

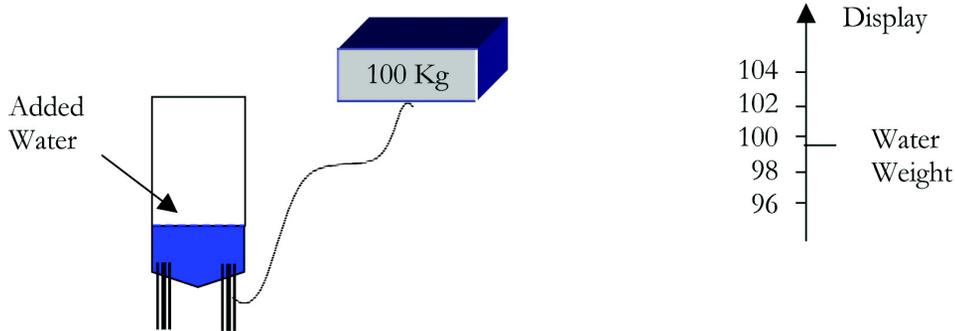
A procedure for defining scale tolerances:

- a. Identify Load Cell Class from the nameplate or other documentation. (For example: Class II)
- b. From the engineering process documentation and SOPs, identify the scale operating range or ranges. (For example: 0 to 14,000 Kg)
- c. Get information of the display resolution. (For example: the display will advance in increments of 2 Kg).
- d. In Table B, find the Load Cell Class and follow across to the weighing range. Below the weighing range, find appropriate maximum permitted tolerances presented in the display resolution. (In this case, two numbers will be identified:  $\pm 1$  for 0 to 5,000 displayed units and  $\pm 2$  for 5,001 to 20,000 divisions)
- e. Multiply the tolerance in the display resolution on resolution value. That will be the maximum permitted scale tolerance. (In our example, the scale display resolution is 2 Kg. Therefore, the maximum permitted tolerances for that scale will be  $\pm 2$  Kg in the weighing range 0 – 10,000 Kg and  $\pm 4$  Kg in the range of 10,001 – 14,000 Kg).

Step 1: Load test weights on top of tank scale.



Step 2: Remove Weights and add 100 Kg water. Added water cannot be exactly 100 kg



Step 3: Add Weight on top of tank. The water addition is not an exact weight.  
Calibration error is introduced.

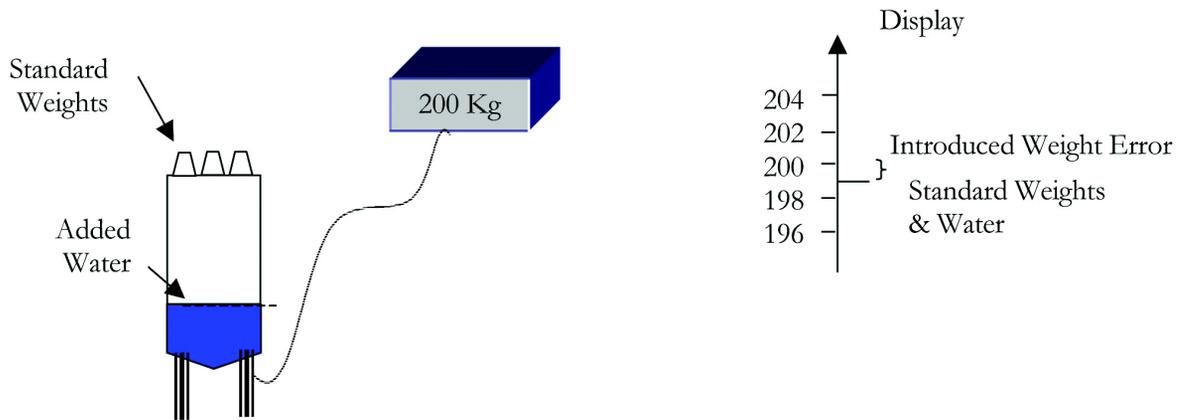


Figure 3. Calibration steps with water additions.

Continued on page 86.

Usually, new and existing process descriptions and equipment specifications are identified in the engineering documentation Functional Description Specification (FDS). Qualification and validation of pharmaceutical processes are based on approved FDS. Qualification and validation protocols are required to verify that selected weighing systems tolerances will not extend over the weighing limits permitted by R&D product development documentation. Dedicated test scripts in the approved protocols are necessitating challenges of engineering calculations in regard to scale tolerances and weighing performances.

In our discussion we explained the imperativeness of interrelation between weighing process limits, scale tolerances, and R&D product development weighing restrictions. An engineering method of identifying weighing system tolerances from load cell classes and display resolutions in relation to weighing process requirements is presented in Figure 2.

Weighing tolerances and calibration limits of scale systems are interrelated and equally dependable. The identified procedure is important for engineering specifications and identification of weighing tolerances. Calibration limits cannot exceed system weighing tolerances. However, in many cases, applied calibration methods require to establish calibration limits narrower than scale tolerances. Properly established calibration limits are a very important factor in cGMP calibration programs. Methods and procedures for defining calibration limits are discussed below.

### Scale Calibration Limits

Calibration limits for scales are functions of the scale tolerances, process requirements, and calibration procedures. Calibration scale limits for Acceptance Tests cannot exceed half of maximum permitted tolerances outlined – *Table B*. Process requirements will be represented by tolerances and accuracies transferred to values of calibration limits. Calibration procedures and methods have an impact on calibration limits. Scale calibration procedures may involve the following two methods:

- Direct placement and removal of standard weights in predetermined fashion.
- Calibration in steps with loading a tank scale with weights, removal of weights, and addition of water to approximate weight of previously placed standards. Loading standard weight again and repeating this procedure by adding water.

Calibration limits for scales calibrated with direct additions and removal of weights shall comply with process tolerances – *Table B*. Large tank scales calibrated with step loading will concede additional errors by introduction of water additions in the calibration procedure.

Scales calibrated with individual weights and additions of water will have calibration limits as per the Table B minus one. Water additions are inconsistent with standard weights. To satisfy requirements for specified scale process tolerances, it is necessary to reduce the scale calibration limits to one resolution of the weight display.

Graphical representation of the above statement justifies the defined scale calibration limits to satisfy the required process tolerances. The water addition cannot be added at an exact required weight. Graphical representation of calibration steps shown below will explain differences between calibration limits and process weighing tolerances.

Figure 3 shows a calibration procedure with water additions. Such procedures are employed for large tank scales when only direct weights additions are not possible. A tank scale of 15,000 Kg requires calibration of 0 to 15,000 Kg. It is not expected to place 15,000 Kg of standard weights on the top of a tank. Weights of water additions will reduce the amount

Number as Displayed or Printed	Number of Significant Digits	Implied Range
341	3	340.5 to 341.4
00341	3	340.5 to 341.4
0341.0	4	340.95 to 341.04
341 EE7	3	340.5 EE7 to 341.4 EE7
3.41 EE-2	3	3.405 EE-2 to 3.414 EE-2

Table A. Examples of significant digits.

of standard weights.

A calibration procedure with water additions reduces the expected outcome of scale accuracy. As shown in Step 2 of Figure 3, water addition is not exactly 100 Kg when the display reads 100 Kg. Therefore, Step 3 of Figure 3 will inherit an

WEIGHING SYSTEM TOLERANCES				
Load Cell Class	Weighing Range (All values in this table are in scale divisions)			
	I	0 – 50,000	50,001 – 200,000	200,001 +
II	0 – 5,000	5,001 – 20,000	20,001 +	
III	0 – 500	501 – 2,000	2,001 – 4,000	4,001 +
IIII	0 – 50	51 – 200	201- 400	401 +
III L	0 – 500	501-1,000	(add 1d for each additional 500d or fraction thereof)	
<b>Tolerances: Not to Exceed – in Scale Display Divisions</b>	<b>±1</b>	<b>±2</b>	<b>±3</b>	<b>±4</b>

Table B. Weighing systems tolerances.

error. With this and following steps, the scale will accept an additional error of one resolution. This error is additive to the scale calibration accuracy. In order to maintain the specified weighing system tolerances, the calibration limits must be adjusted to compensate for water addition errors.

Standard calibration procedures for large scales include loading and unloading steps. To maintain weighing tolerances as specified in Table B, calibration limits need to be established accordingly. For example, the tank scale process tolerances are identified as  $\pm 2$  display divisions. The process tolerance for such scale will be  $\pm 4$  Kg. If that tank scale is calibrated with the water additions, then calibration limits should be set to  $\pm 2$  Kg. If the tank scale is calibrated with the standard weights only, then calibration limits will be  $\pm 4$  Kg.

Engineering process documentation for scale systems needs to consider calibration methods for weighing tolerances. Reductions of calibration limits are not always possible. If the required weight tolerances are equal to one scale resolution then water additions will necessitate zero deviation in calibration tolerances. Absolutely accurate scales are not possible to consider. Therefore, adjustment to weighing processes limits could be contemplated after evaluation of the entire process system and all options.

It is important to remember that weighing process limits and properly calibrated scale tolerances can not permit actual weighing additions to extend above or below the R&D product development limits. If changes within process and calibration limits of scales will not guarantee that weighing additions will be maintained within R&D product development limits, then a new weighing system must be considered.

In the process of scales calibration, the display readings could slightly fluctuate from the weighing standards. Deviations of calibrated readings from standard weights within defined tolerances are acceptable. Requirements for scale adjustments per “as found” data are outside of our discussion. However, in most cases, fluctuations of calibrated data less

a scale cannot be verified for processes utilizing weighing additions significantly larger than one or two tests.

A simplified calibration check could be performed on the bases of scale capacity and process requirements. Such methods could be named as Functional Certification.

Loads and test weights for Functional Certifications shall be established – Table C. Table C could be utilized for setup of weighing systems calibration ranges. Non-critical scales utilized for measurements of raw product storage, inventories, etc. may not be required for calibration at the full range. That issue must be carefully examined to make sure that a range that is not calibrated will have no impact on the finished product.

## Conclusion

This article is written to explain methods and procedures for identification of process weighing tolerances and corresponding calibration limits for process scales. The described methods and procedures could provide simple tools for setting up new weighing process specifications and verification of existing scale capacities in regard to process requirements.

The actual calibration methods and calibration procedures are subject to the established metrology standards and are not covered in this article. Standard weight selections and standard weight classifications are subjected to NIST standards. The sources for metrology procedures are identified in the bibliography.

Specified process weighing tolerances and calibration limits must guarantee that properly functional calibrated systems will keep weighing additions for compounding or formulation processes within the established R&D product development weighing limits. Specification for process weighing tolerances and calibration limits should consider safety factors of small fluctuations in the scale’s calibration and performance. “As found” calibration data outside of permitted weighing tolerances shall trigger an investigation of all products produced between the date of the last calibration and current date of detected calibration out-of-limits.

Reliability of weighing systems is critical for finished product quality and manufacturing QA program. Proper selection of equipment with matching tolerances and calibration limits will minimize possibilities of incorrect weighing additions in compounding and formulation processes. Incorrect weighing additions produced by the system will generate unrecoverable cost of rejects and rework. Improperly setup weighing systems could lead to poor product quality and mistakes in product releases. Pharmaceutical products made outside of approved specifications could be harmful to patients and will set off grave implications to a firm if released on the market by mistake.

## References

1. Handbook 44, 2000 Edition.
2. Specific Technical Guidelines from NVLAP Calibration Laboratories Technical Guide, <http://ts.nist.gov/ts/htdocs/230/235/h143/intro.htm>.
3. Specifications and Test for Strain Gage Pressure Transducers. ISA=37.3-1982(R1995).

## Glossary of Terms and Definitions

**Calibration of Weighing Device** - Applying known weights to the scale for verification of accuracy and tolerances over portion of the weighing range.

**Capacity** - The scale rating defined by the maximum load for

Test Weights and Load Requirements for Scale Certifications		
Scale Capacity	Test Weights	Minimum Test Load
0 to 150 Kg	25 Kg weights	@ operation capacity + 25 Kg
151 to 1,500 Kg	25 Kg weights	@ 75% operation capacity + 100 Kg
1,501 to 20,000 Kg	25 Kg weights	@ 50% operation capacity + 200 Kg
20,001 Kg+	25 Kg weights	@ 25% operation capacity + 300 Kg

Table C. Test weights and load requirements for scale certifications.

than 60% of tolerances will not necessitate adjustments.

## Calibration Checks

Usually calibration checks are considered as a first step of a batch process to gain an additional assurance in a scale performance. Those checks are accomplished by placing one or two weights on an empty scale and comparing readings of the display to the weights value. With this method, performance of

which the system is designed.

**cGMP** - current Good Manufacturing Practice

**FDS** - *Functional Description Specification*.

**Load Cell** - A device (electronic, hydraulic, and pneumatic) that produces a signal proportional to the applied load.

**Scale Divisions** - The smallest indication of the difference between two consecutive weighings.

**Scale Sensitivity** - The value of test load that produces a specific minimum change in the position of rest on the indicating display.

**Specifications of Scale Class** - A requirement usually dealing with the design, construction, and making of a weighing device.

**Tolerance** - A value fixing the limit of allowable error or departure from true performance or value.

### **About the Author**

Yefim S. Gudesblat, PE is presently employed by Engineering Solutions, Inc. He is responsible for all activities in the electrical and instrumentation department. In 1971, Gudesblat completed his studies in physics and electrical engineering technology in Odessa, Ukraine (Formally USSR). He is a registered Professional Engineer in Pennsylvania, North Carolina, and New Jersey. Gudesblat has 20 years of experience in the pharmaceutical industry and several articles in leading technical magazines, including **Pharmaceutical Engineering**. He was employed by Wyeth-Ayerst Laboratories and Johnson & Johnson – Merck. Presently, Gudesblat works on projects for many pharmaceutical and biological companies.

Gudesblat can be reached at 1-856/489-2585 or [gudesby@labs.wyeth.com](mailto:gudesby@labs.wyeth.com). 