Manual Inspection Booth Description

MIB-80™, MIB-90™ & MIB-100

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MIB-100 A STANDARD MANUAL INSPECTION ENVIRONMENT FOR OBTAINING ACCURATE VISIBLE CONTAMINATING PARTICLE INSPECTION DATA

INTRODUCTION

Injectable product batches must satisfy two different USP particle contamination assays prior to acceptance for sale and use. The first of these is a small-scale destructive assay for sub-visible particles. Due to the small sample size of this assay, it is a reliable indicator of systematic problems**,** problems that exist uniformly throughout the batch. This type of problem is typical product/container, product/stopper interactions or product formulation and/or product delivery problems. The second of the USP particle contamination assays the 100% visible particle inspection addresses the incidence of random visible contaminating particles. Due to the random nature of the visible particle contaminants, their incidence rate can only be accurately measured and controlled by a 100% inspection of the entire batch. A corollary of this conclusion is that the present USP batch release Assay is insensitive as an indicator of batch quality improvement.

According to GMP regulations any new method or procedure must be shown to be as good as its predecessor before it can be used on a USP listed product. For visible particulate the preceding visible contaminating particle inspection is that of the single container inspection by clinical personnel at the injection site. This GMP requirement means that any visible particle inspection method or mechanism must be shown to be as effective as the single container inspection for visible contaminants performed by clinical personnel at the inspection site. Accurate evaluation of the capability of a skilled inspector inspecting a single container determines the minimum acceptable performance for any other inspection method or mechanism.

The inspection for visible contaminating particles is a biophysical measurement. To achieve standard sensitivity and statistically accurate data the conditions and implementation of this inspection must be accurately described and reproduced. This includes adjustment of the near vision capability of the inspectors to the normal equivalent of 20/20 vision and adequate training before their use on a USP listed product. The level of light intensity at the inspection point affects particle size detection sensitivity. Another factor, which must be considered, is the decrease in contrast sensitivity with the age of the inspector. This difference can be reduced to negligible dimensions by the choice of the selected light intensity. At 550 ft-candles inspectors up to 65 years old can function accurately. Another factor contributing to the choice of 550 ft-candle illumination intensity is the need to separate visible and sub-visible contaminating particle data. For this need the 550 ft-candle illumination intensity is a convenient choice.

The usefulness of fire preceded by millennia the scientific description of its actions or its accurate measurement. So too, the application of injectable products has not waited for the development of the present array of scientific methods and measurements. The clinical use of injections has grown from a single hazardous medical episode in the

1820 Cholera epidemic to treat patient dehydration as a cause of death to a major part of the present medical armamentarium.

The scientific and statistical methods needed to measure and analyze the incidence of visible particle contamination started to become available during WWII. 1980 saw the first publication of replicable measurements if visible particle contamination expressed as probability of detection. At the 2004 PDA Annual meeting the measurement of the size of visible particles in sealed containers was finally linked to the National Dimensional Standards maintained at the NIST, the National Institute of Standards and Technology. This final link-up means that the results of any visible particle inspection method or device can now be firmly linked to National and International standards. The incidence of visible particles in batches of injectable products can now be measured and accurately replicated from one measurement site to any other when the conditions of the measurement are replicated.

BASICS: LIGHT INTENSITY

Data accuracy for visible contaminating particles has been shown to be sensitive to the type and intensity of the light at the inspection point inspection. To eliminate this source of variability from the data, a light intensity feedback stabilized 1 cubic foot inspection volume was developed and patented, U.S. 5,940,176 August 17, 1999. This Patent describes the achievement of a volume in space in which the variability of light intensity is maintained within ±5%. This variability is the least discriminable amount that human eyes can detect. Also applicable to this inspection environment is U.S. Patent No. 5,940,176 dated Aug 17, 1999 with other patents pending.

The volume of controlled light intensity has been achieved with the use of two illumination sources, each one describable as an odd function of illumination and distance from the source. In the distance between the two lamps an even function of illumination intensity centered on the midpoint between two opposing sources is achieved. The fluorescent lamps employed are the new extended life lamps with improved color rendition capability excited by ultrasonic ballasts. The ultrasonic excitation eliminates the effect of strobed images that occur at a rate twice that of the line voltage.

All fluorescent lamp systems require a warm-up period before stable operation commences. **To assure that the selected light intensity is accurately delivered, the system commences operation only after the warm-up period has ended.** The selected light intensity is maintained by a feedback controlled light intensity stabilization system. After the warm-up period the delivered light intensity is **continuously monitored** to assure accurate delivery of the **selected** 550 ft-candle intensity. Light intensity stabilization based on direct evaluation of the lamp output has been selected because it inherently provides better accuracy than indirect stabilization using measurements of driving current or voltage.

Two controlled illumination systems **in an opposed vertical configuration are** employed to generate a stabilized illumination volume. The light intensity delivered by

both systems is summed to provide 550 ft-candles at the vertical center of the inspection environment. This “in regulation” condition is indicated with a digital output and **the activation of a green** pilot lamp. If at any time the illumination system cannot operate at the 550 ft-candle set point, a message is displayed to the operator indicating that a **fluorescent** lamp is operating below the controlled set point. When the “out of regulation” condition occurs, a red screen is displayed and a message appears indicating lamp replacement is required. No further inspection data is accepted until the replacement has been made. The choice of light intensity measurement as the feedback **control** signal results in the independence of light intensity during use and also when lamps are replaced. This feedback signal choice **makes the lighting system independent of the expected variability that is encountered in the replacement process.**

The light intensity at the inspection point was selected on the basis of I.E.S. recommendations is 550 ft-candles ±5%. This value minimizes the interference fringe between ‘visible’ and ‘sub-visible’ particle sizes. The selection also minimizes the loss of contrast sensitivity with aging. Published data indicates a reduction to negligible magnitude for this effect up to the inspector’s nominal age of 65.

BASICS: PARTICLE SIZE VERSUS PARTICLE REJECTION PROBABILITY: A NEW, STABLE TRANSPORTABLE STANDARD SET

The test parameter that has made possible replicable measurements of the incidence of visible contaminating particles is the detection probability of identified sealed containers. Since this measurement uses the probabilistic response of human beings, accurate replicability requires the mean of many responses. Although the basic measurement parameter is probability of detection, a broadly determined calibration curve, which relates particle detection probability to the maximum dimension of a particle, provides a more desirable production control measurement. This conversion also provides a traceable connection between visible particle contamination measurements and the National dimension standards maintained by the National Institute of Science and Technology. Such a dimensionally stable set is available from Phoenix Imaging.

The accumulation of data from multiple inspection sites collected under well-defined conditions will generate a truly standard international curve relating maximum particle size to particle detectability. With this curve visible particle contamination data can proceed beyond a rough comparison of results to the correlation of equal sensitivity measurements. **Initial data for this standard curve has been published. As more data, generated in the defined experimental conditions, becomes available, the accuracy of the calibration curve will continue to increase.**

This standard curve will provide an essential transportable standard with which the incidence rate of visible contaminating particles in sealed containers of injectable products can be accurately harmonized. Such harmonization will provide a level playing field for the measurement of the incidence of visible particle contamination in injectable products independent of the measurement site.

BASICS: EFFECT OF FATIGUE ON MANUAL DETECTION PROBABILITY

The detection of visible particles in injectable products is a trainable human skill. As in the performance of any trained human skill, the incidence of fatigue decreases performance effectiveness. Knapp (1980) reported that fatigue could decrease the Reject Zone Efficiency of an inspector by as much as 30%. When the movements required of an inspector do not consider the physical size of the inspector, the duration of work time before the onset of inspector fatigue can vary widely. An efficient manual inspection requires normalization of the physical movements of each inspector.

BASICS: NORMALIZATION OF INSPECTION FATIGUE

The Phoenix Imaging MIB series of standard manual inspection environments for accurate visible contaminating particle inspection data, shown in Fig. 1, contains a 1 cubic foot volume in which the delivered light intensity, following IES recommendations, is 550 foot-candles ±5%. The Probability of Rejection (P_R) for a 95 µm diameter particle is about 70% when using 550 ft-cd (~5920 Lux). In this inspection environment all motions are scaled to the physical dimensions of the inspector. The individual parts of this inspection booth are adjustable, tool free, to match the inspector's height and reach as described in the following sequence of actions for a production inspection. The use of the inspection procedure, outlined below, by a well-trained inspector results in a smooth flow of inspected containers using tactile location and placement of containers. The work output of the inspector is optimized: all the inspection motions are scaled to the physical size of the inspector thus normalizing the effects of fatigue.

The inspection procedure includes a forearm extension of the hand grasping the container to position the container in the light controlled inspection volume. To guard against the occurrence of repetitive motion injury resulting from the extended forearm position usually encountered in manual inspection, an adjustable forearm rest is provided. The rest is positioned to match the physical size of the inspector thus eliminating the usually encountered stress in this inspection.

SEQUENCE OF INSPECTION MOTIONS

1) The seated eye height of the inspector is adjusted to the centerline of the controlled illumination volume as shown on the Booth.
2) The center of incoming material tray and the inspected container tray is adjusted to be at the elbow height of the seated inspector.
3) The 3 dimensional inclination and position of each tray is adjusted to provide full access to the contents of the tray by the movements of the inspector's wrist and forearm only.
4) Before inspections commence, the inspector enters the complete identification for the inspection. This includes the inspectors ID, date, time, product and potency and the quantity to be inspected. Following review and approval by the supervisor, the control panel is Green and control reverts to the inspector.
5) The inspectors right arm is used to select a container from the right tray, the un-inspected container tray, and to bring it to the first of two inspect positions, the center of the white **inspection** background position. The use of an inkjet

paper sheet with a brightness index of 92 or higher is recommended for this purpose.

6) At the inspect position, the inspectors forearm rests on the padded support whose position is adjusted to support the forearm when the container is positioned at the height center of the accurately illuminated test volume. The width of the forearm rest provides support during both the white and black background inspections. NOTE: The padded rest is positioned so that the forearm is supported with the container to be inspected positioned at the center height of the illuminated volume.
7) At the end of the container positioning motion, the container is agitated in a conic motion ending with the maximum deceleration to a final stop. The inspector is trained to achieve maximum deceleration below that at which cavitation bubbles appears as a condition for a good inspection.
8) The end of the white background inspection is signaled to the inspector when the face of the signal panel turns red.
9) The inspector has three action choices at the end of the white inspection period: Accept, Reject and third No decision, repeat cycle.
10) In the event a White Background Reject decision has been made, the inspected container is transferred to the left hand for disposition in the Reject Tray and the next container is selected by the right hand and transferred to the inspect position and steps 6-9 are repeated.
11) Following a white background Accept decision, the inspector moves the container position by the width of the white background to a black **background** position and initiates the black background inspection as in Steps 6 through 9 with a Green Panel display.
12) At the end of the black background inspection period, the panel is red and the inspector again makes one of three decisions: Accept, Reject, or Repeat cycle. Repeat cycle is used when no decision has been made in the planned inspection time. In the event a Black Background Accept or Reject decision has been made, the inspected container is transferred to the left hand for disposition in either the Accept or Reject Tray and the next container is selected by the right hand and transferred to the inspect position for the White background Inspection and steps 6-9 are repeated.
13) For test group validation demonstrations the individually identified containers are presented to the inspector in randomized order. Lint free gloves are needed to maintain each container surface free of finger oils during randomization and serial number recording. The accept/reject record of each container in each inspection by each inspector is the data required.

INSPECTOR EVALUATION PROCEDURE

Evaluation of the effectiveness of an inspector or a group of inspectors can be made with a serial numbered test group of 248 containers. This test group should be broadly representative of the entire visible particle contamination spectrum from absolutely clean to those containers with grossly contaminated 'must reject 'visible particles. The 'must reject' group is the group of containers whose individual rejection probability is equal to 0.7071 or greater. To assure production line equivalent inspections, this 'must reject' group is restricted to 62 containers, 25% of the total number of containers in the test group.

The test containers can be selected in a preliminary test using the pooled inspection results of a group of 5 experienced inspectors who inspect once each 400 randomly selected containers from current production and 100 containers from the retained reject library. The containers in the test group are selected on the basis of the total number of rejections from the pooled results of all inspectors. 62 of the containers are from the group that has not been rejected in any inspection, 62 containers are selected from the test group of containers that have been rejected once. The next 62 are selected from the containers that have been rejected 2 or 3 times in the five inspections. The last group of 62 containers is selected from thee group that have been rejected 4 or 5 times in the initial screening inspection. Incorporation of the calibration group of NIST traceably dimensioned stainless steel microspheres provides the means with which the sensitivity of the inspection can be checked against the proposed National Standard.

A sequence of 10 inspections per inspector provides adequately sensitive test results. An analysis of the inspection data has been performed effectively using Microsoft Corporations Excel® or similar spreadsheet program. When an Excel® is used, line numbers can represent each container. Representing accept signals by zero and reject signals by 1 makes it possible to us row additions to calculate the total number of rejects per container for an inspector or for the entire inspection group. The experimental rejection probability is calculated as the total number of rejections per container divided by the total number of inspections per container.

The number of containers in the Accept and Gray Zones is determined by the number of containers in the test group whose rejection probability is less than 0.7071. The number of containers in the Reject Zone is equal to the number of containers whose rejection probability is equal to or greater than 0.7071.

The effectiveness of an inspector or a group of inspectors is determined by the Reject Zone Efficiency, the RZE. RZE is calculated as the sum of the rejection probability of each Reject Zone container divided by the number of containers in the Reject Zone. A Reject Zone Efficiency equal to or greater than 0.85 should be obtained.

Similarly, the False Reject Rate is calculated as the sum of the rejection probability for each container in the Accept and Reject Zones divided by the total number of containers determined to be in these zones. An upper limit of 0.10 should be obtained for this reject loaded group.

The procedure described above requires manual entry of the serial number of each container in each inspection to assure secure correlation of container number and inspection results. Where such an evaluation is planned to be used as a both a periodic re-certification procedure and a means to evaluate new hires, a more automated alternative should be considered.

Following a comparison of alternative inspector evaluation methodologies, Knapp recommended the use of a Cartesian plot of the individual inspector's capability in the inspection of the standard test group. (See the Marcel Dekker "Liquid & Solid Borne Particle Measurement Handbook edited by Knapp, Barber and Lieberman for details). Such a plot uses the RZE score of the individual inspector as the independent variable. The RAG, the undesired reject rate in the Accept and Gray Zones, is the dependent variable. Around each plotted point, the probabilistic variability in both coordinates is plotted. An RZE of 0.85 and an RAG of 0.10 can be expected for an experienced inspector.

The MIB-80™, MIB-90™, and MIB-100™ have very uniform inspection volumes. The inspection volume is the region that the inspector can position a product within a constant light intensity. The Figure below shows a fairly flat intensity surface over a volume of approximately 10 liters where the intensity remains within ±5% of the center value.

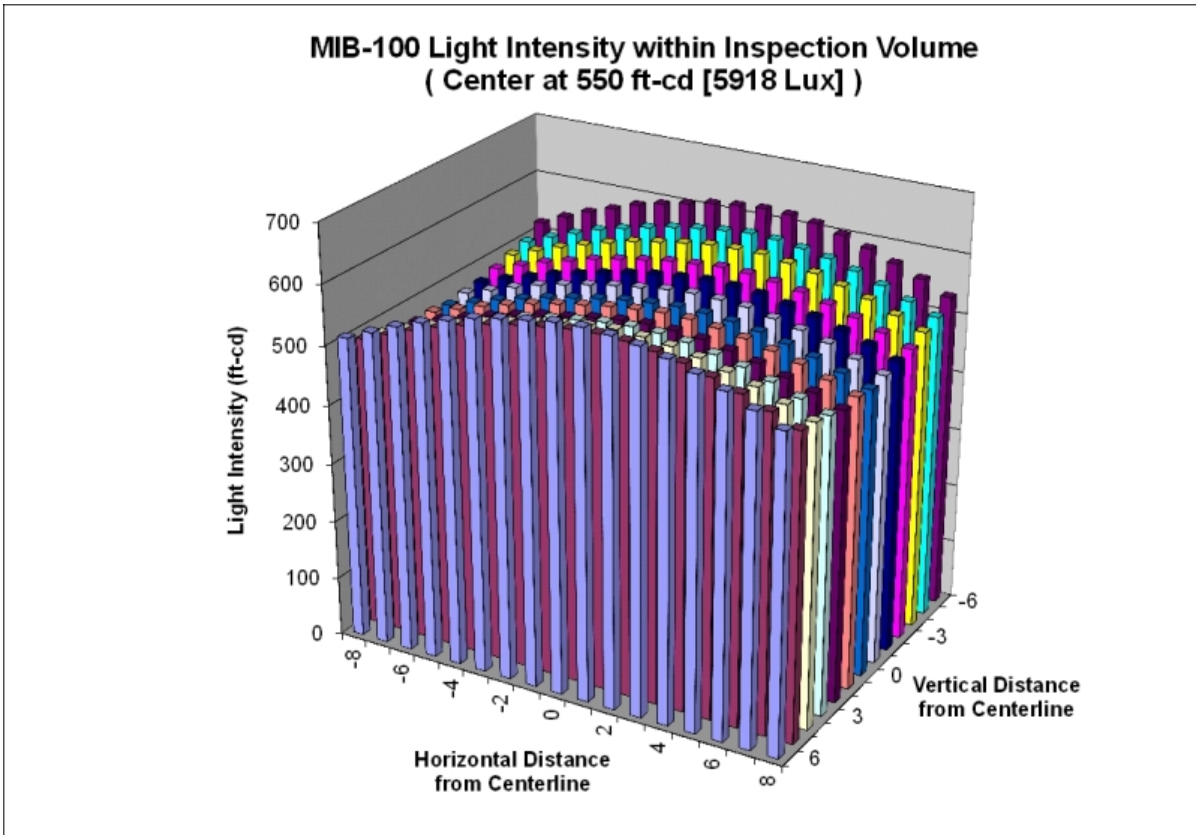

Figure 1. MIB-100™ Light Intensity Map

When compared to the typical top lighting inspection booth configuration it is easy to understand why there is so much variability in inspection results. The typical top lighting booth has two lamps positioned above the inspection background. The light intensity decrease rapidly as the inspection point moves away from the light sources. This is described as a “waterfall” configuration because there is a rapid change in light intensity. Figure 2 below is a Light Intensity Map for a dual 40W lamp configuration.

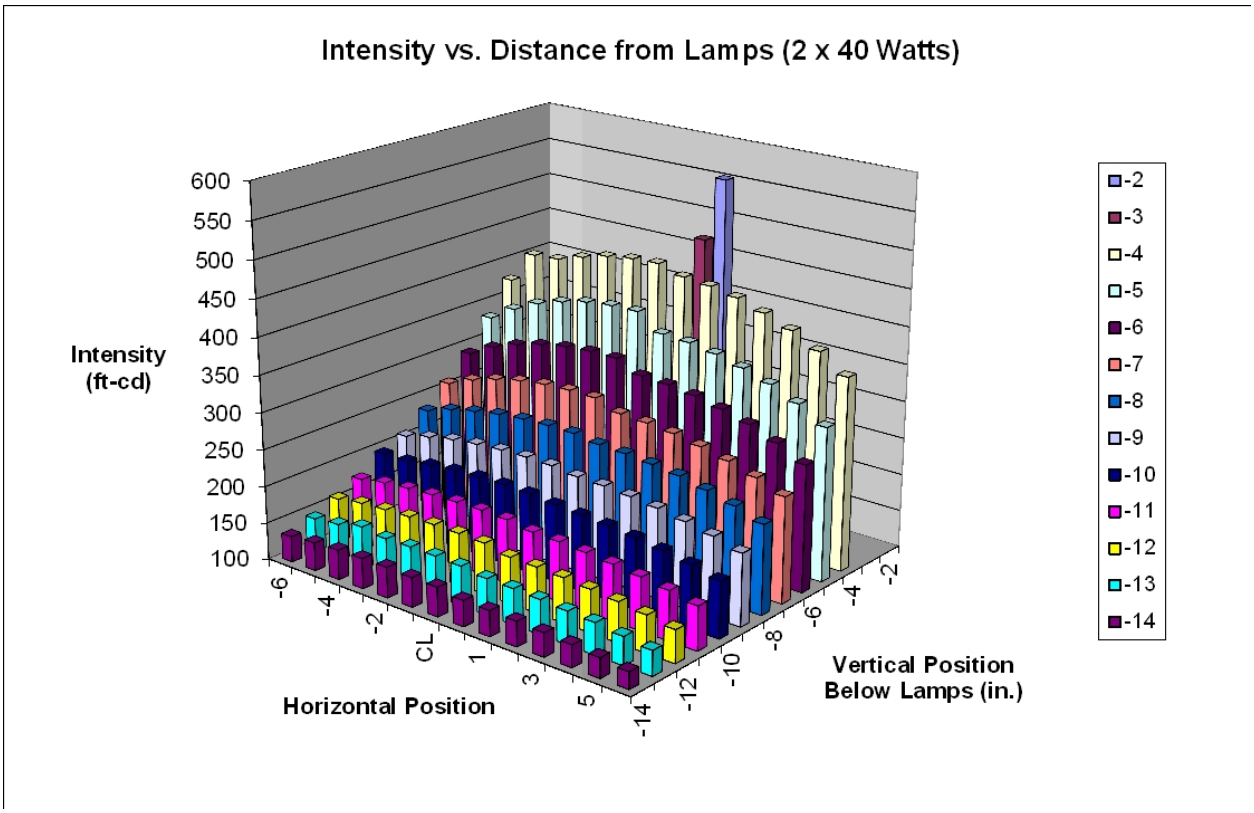

Figure 2. Light Intensity Map of Standard 40W Top Lighting Inspection Booth

The figure shows the light intensity as a function of position in the horizontal and vertical locations relative to the center of the White/Black background. The inspector must be about 8” below the lamps before the light intensity becomes more gradual. It is very difficult to perform an inspection in this type of booth without a large change in the light intensity. Since the Probability of Rejection (P_R) is directly proportional to the amount of light in the inspection volume a consistent P_R is impractical to achieve. It is not uncommon to observe an inspector move the product closer to the light source when they see a suspect particle. When the product is positioned closer to the light source the PR increase dramatically leading to inconsistent inspection capability from Lot to Lot and inspector to inspector.

THE PHOENIX IMAGING MIB-100,
A STANDARD VISIBLE INSPECTION ENVIRONMENT

FIGURE 3

The Phoenix Imaging MIB-100™ provides a standard manual inspection environment for accurate visible contaminating particle inspection data with a PLC pacer function. This model is shown with optional side shelves and top shroud to reduce the effects of ambient lighting on the inspection volume. The MIB-80™, MIB-90™, and MIB-100™ use dual precision power supplies with active feedback monitoring of lamps to maintain a constant lamp output. The lamps operate at 55 KHz for a flicker free inspection environment.

THE PHOENIX IMAGING MIB-100™,
A STANDARD SYSTEM CONFIGURATION

FIGURE 4

THE Phoenix Imaging MIB-100™ in the standard configuration with optional side shelves for production environments. The standard configuration has a Corian® solid surface armrest with a curved front. This allows the inspector to position closely to the inspection volume without straining forward, thus reducing the effects of physical fatigue. The side shelves can be positioned so that the inspector has minimum reach for incoming and inspected products. The side shelves have numerous adjustments so that the trays can be positioned for maximum operator comfort.

DESCRIPTION OF KEY COMPONENTS OF MIB-100 INSPECTION BOOTH (see Figure 4)

1) Main Structure of MIB-100 is constructed of anodized aluminum.

2) Operator Interface Panel with touch screen interface allows data entry and display of results.

3) Adjustable Container Input Tray. This item is normally configured to the customer's requirements for tray size.

4) Adjustable Arm Rest. The armrest can be adjusted to travel both vertically to accommodate the desired position of the inspector. The height is normally set so that the container is located in the center of the uniform illumination volume when the forearm is slightly extended into the booth.

5) Adjustable Inspected Material Tray. This item is normally configured to the customer's requirements for tray size. The trays can be adjusted to the desired inclination, height, horizontal position and angle to maximize inspector comfort without the use of tools.

6) The Vertical Adjustment for Tray Support Arms. This allows the support arm for the Horizontal tray support arm to be positioned vertically on the booth exterior.

7) The Horizontal Tray Position Adjustment. This device allows the inspector to slide the position of the tray closer or away from the main inspection enclosure. As with all the other adjustments on the MIB system no tools are required.

8) Horizontal Support Rail for Armrest. This rail provides extra support for the Corian Armrest and prevents the armrest from rotating under pressure.

9) Adjustable Front Screen (not shown). The top front screen can be adjusted to accommodate inspectors of various sitting heights. The screen height is adjusted to block visibility of upper source light from entering inspector's vision.

10) The Tray Inclination Adjustment. This device allows the inspector to incline the trays to the desired angle to reduce fatigue. As with all the other adjustments on the MIB system no tools are required.

11) MIB locking casters. The front caster are locking so that when in position prevent the booth from moving.

12) Replaceable White/Black Inspection Background. This screen is mounted on a flat black polycarbonate sheet with Velcro attachments. The screen can be easily replaced if it is damaged. The White background is a diffuse white painted aluminum and the Black background is a special diffuse black painted background. Both provide high contrast with low glare.

SEQUENCE CONTROL AND DATA RECORDING

The following information describes control of the inspection sequence, data recording and data transfer of the MIB-100 Manual Inspection Booth.

STEP 1: TURN-ON

Power up the PLC by depressing the push button on the left side of the display panel. The first screen to appear when initializing the PLC is the Title Screen. After approximately 20 seconds an orange screen will appear instructing the operator to wait 15 minutes for the lights to warm up.

STEP 2: STARTING CHECK

A red flashing "Lamp out of regulation" screen indicates a bad lamp(s). Turn the power off and replace the lamps in pairs (either the top two lamps or the bottom two lamps). The sequence will start again when power is applied. If the lamps are “in regulation” the system will proceed to the next step.

STEP 3: MAIN SCREEN

The following screen is the Main Menu. This menu allows the operator to alter the settings, initialize inspections and obtain results from those inspections.

STEP 4: SET-UP MENU

By selecting the Settings button from the Main Menu the Set-Up Menu will appear. From here the operator can select the type of inspection to be performed, change the time of the inspection and turn off the lights to restart the system.

4.1 Select Inspection Type to choose either Light/Dark Inspection or Gray Card Inspection.
4.2 Assign rejection categories to the numeric keypad

STEP 5: TIMER SETTINGS

Select Timer Settings to change the actual time of the inspections. Touch the number to the right of the three timer options to select the time desired. All time intervals are in 1/10 seconds. For example, by selecting "50" your inspection time will be 5 seconds. After choosing the time, select the arrow button to enter. Select the CLR button to start over and re-enter time.

STEP 6A: OPERATING START WHITE/BLACK INSPECTION SEQUENCE

When the proper settings are complete select START to begin the inspection. If Light/Dark Inspection is selected the light background will be tested first and then the dark background. While testing the display will countdown the test time selected. After the light background inspection, the dark background inspection screen will automatically appear. The operator can opt to start the dark inspection or retest the light background, if needed. If a defect was detected on the light background select Light Defect and the system will automatically bypass the dark inspection and return to the light test to continue. If no defect was found in the light test start the dark

inspection. When complete the Provide Judgment screen will appear prompting the operator to select "Good" or "Bad." A retest of the dark inspection may be selected at this point, also. After indicating whether a defect was found or was not found the system will return to light test mode.

STEP 6B: OPERATING START BLACK/ WHITE INSPECTION SEQUENCE
This sequence is similar to the White / Black inspection sequence except the inspection begins with the Black background inspection.

STEP 6C: OPERATING START SINGLE 18% GRAY BACKGROUND
If Gray Card Inspection is selected the Provide Judgment screen will automatically appear after each testing.

STEP 7: SHIFT END REPORT
Note that at any time during the testing you may check the status of the results by selecting the Main Menu button.

When testing is complete return to the Main Menu to review the results. Select main screen to copy recorded data from the Results screen. The Results screen will provide the operator with the total of "good" and "bad" and totals in each defect category listed. Record results or, select Reset to clear the current count categories.

MIB-80 vs. MIB-90™ vs. MIB-100

The MIB-80™ and MIB-100™ are similar in look and operation except that the MIB-80™ does not have a PLC operator interface. The MIB-80™ is designed as a lower cost option of the MIB-100™ without the inspection pacing function and product counting function. The MIB-90™ has all of the features found in the MIB-100™ with a few others. The most noticeable feature is the large stainless steel armrest with protective side shrouds. The system also provides an easy pass-through design that eliminates the sides of the inspection area. The MIB-90™ uses hydraulic lifts to raise or lower the entire booth for operator ergonomics because the stainless steel armrest is mounted in a fixed position.

Physical Features:
Main Enclosure: 34.5” W x 28” D x 68.5” H, [876mm (W) x 711mm (D) x 1740mm (H)]
175 lbs. [79.3 Kg]
Corain Armrest: 53” W x 10.75” D x 4” H, [1346mm (W) x 273 mm (D) x 101 mm (H)]
49 lbs. [18.14 Kg]

Options:
2 sided Foot Switch (Quick start inspection sequence / Results), Straight Front Armrest, JP Option (Incandescent lamp for 10,000 Lux), Audible Alarm, Moveable Footrest, Booth Hydraulic Lift Kit (raises or lowers booth 300 mm range)