Connecting People, Science and Regulation ®

Technology Update

Automated Inspection

N.E. Chapter - PDA

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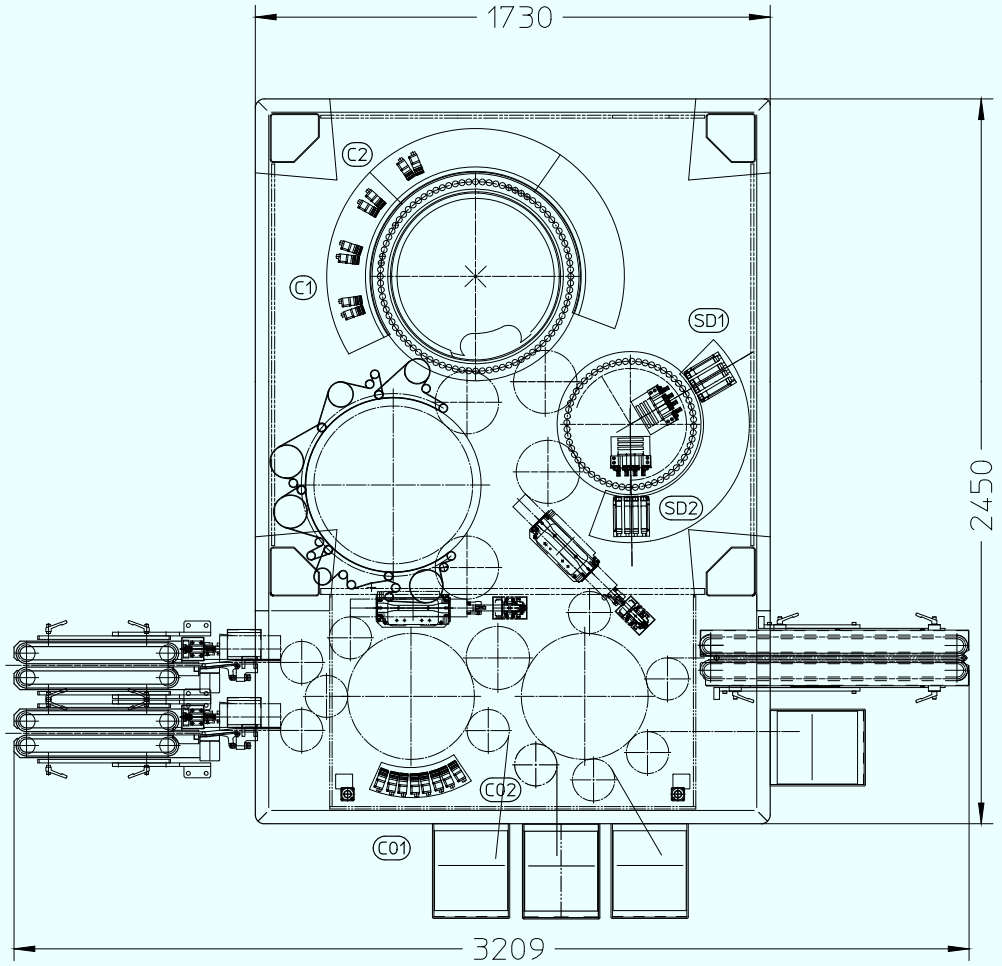
Eisai Machinery

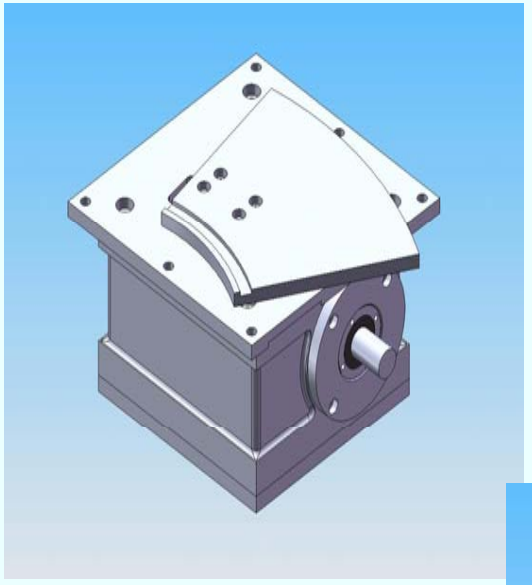
The use of an automated inspection machine is not only important for assurance of final product quality but also for evaluating a process in real time.

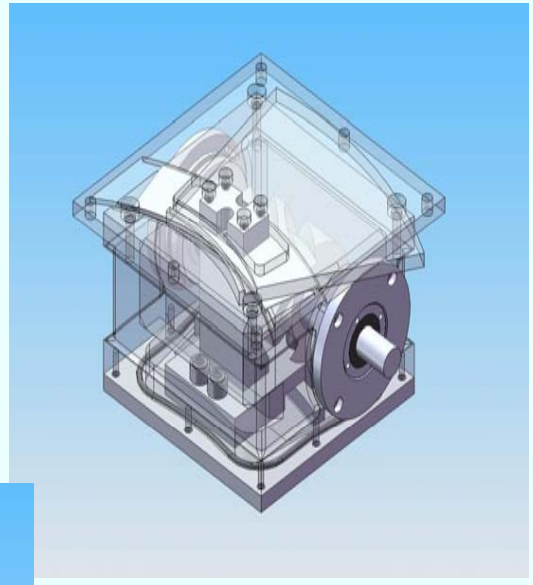
The ability to detect and quantify types of defects (whether process or component related) and then take corrective actions to eliminate or minimize such defects is essential for process optimization.

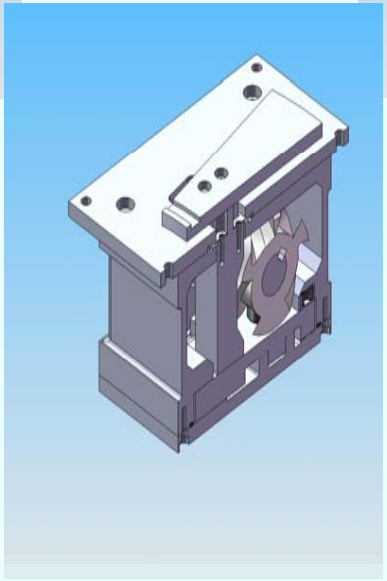
Increased Machine Capacity



36,000 containers per hour

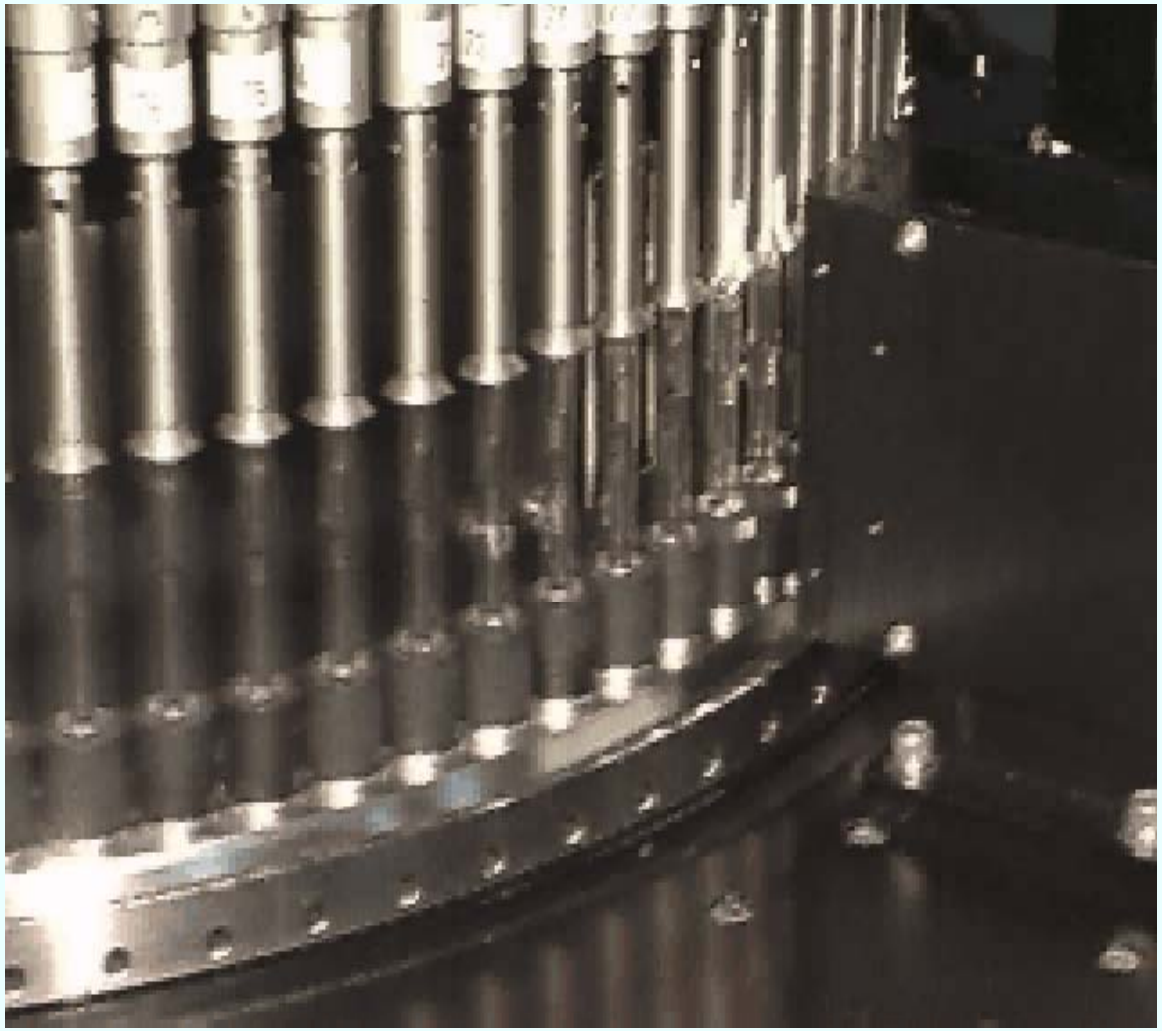






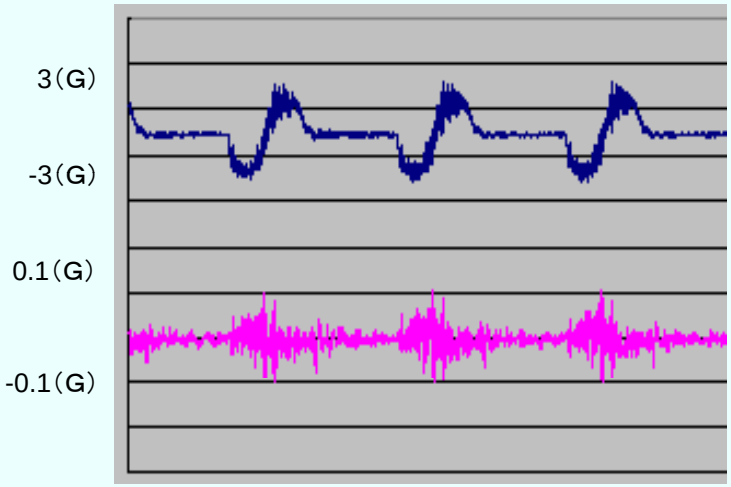
To maintain the same number of images for 300ppm and 600ppm, new oscillating drives were developed.

New - Oscillating Drives



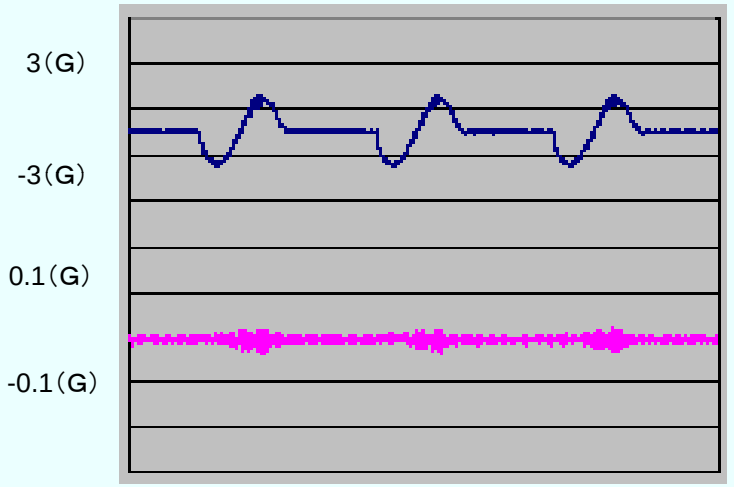
Oscillating Drive Motion

Oscillating Drive



Machine speed 300ppm

New Oscillating Drive

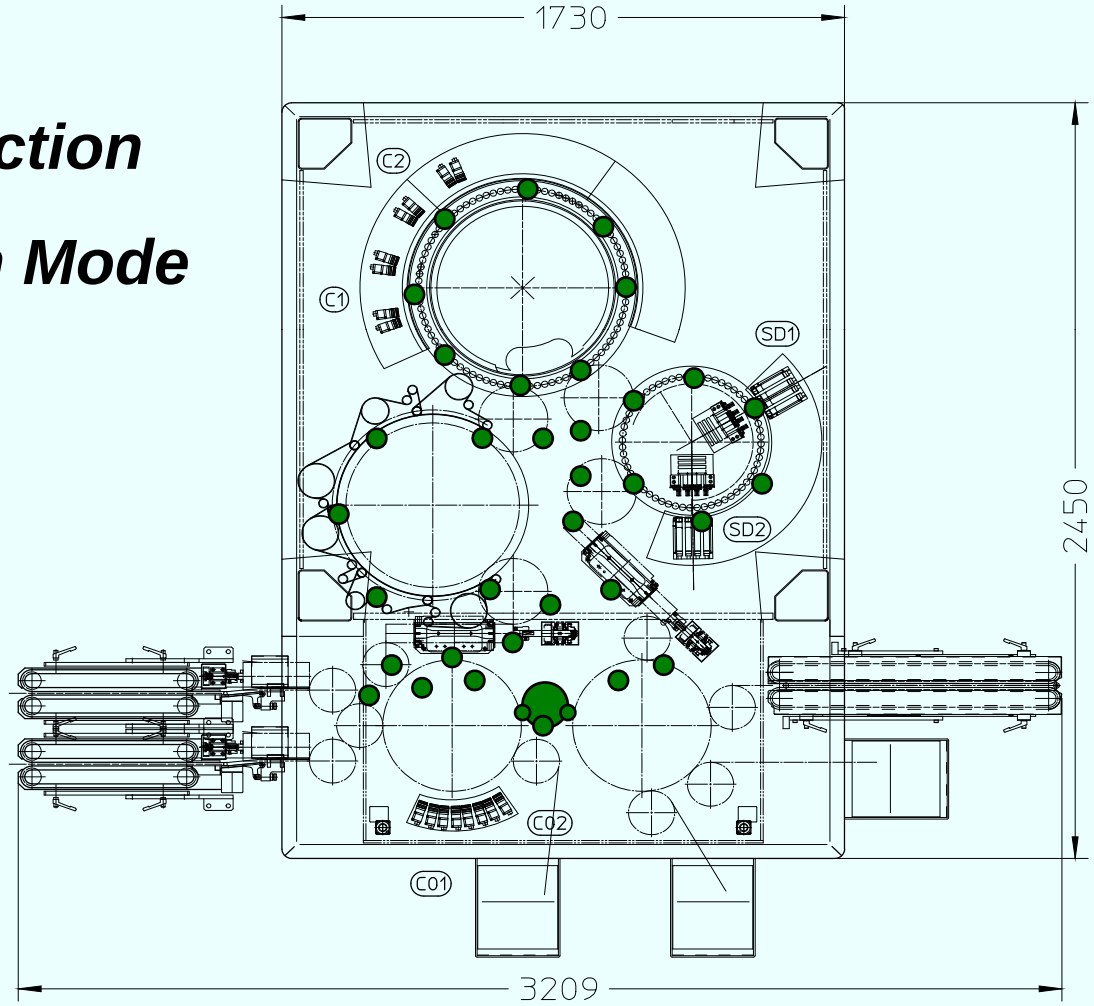


Machine speed 600ppm

Reduction in Vibration

Increase in Sensitivity

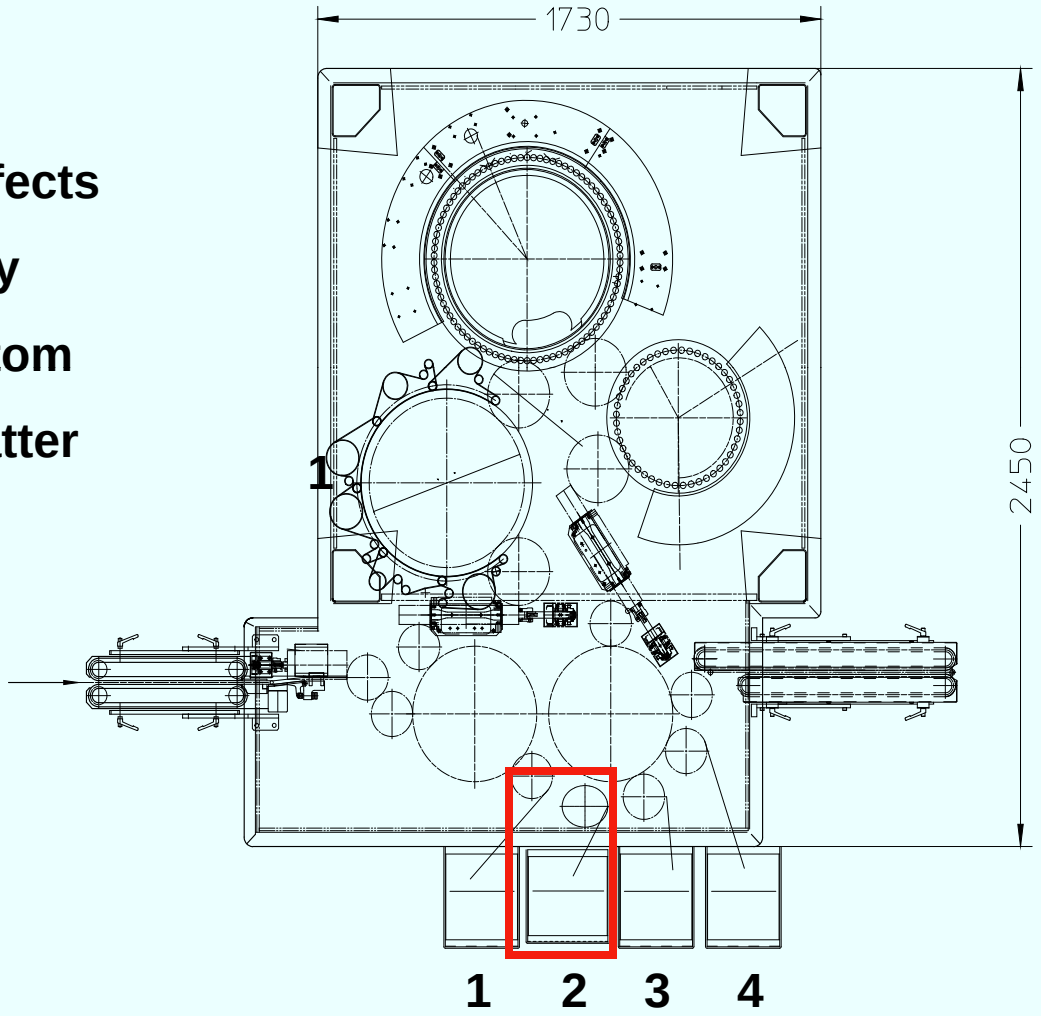
- ***Automatic Re-Inspection***
- ***Complete Validation Mode***



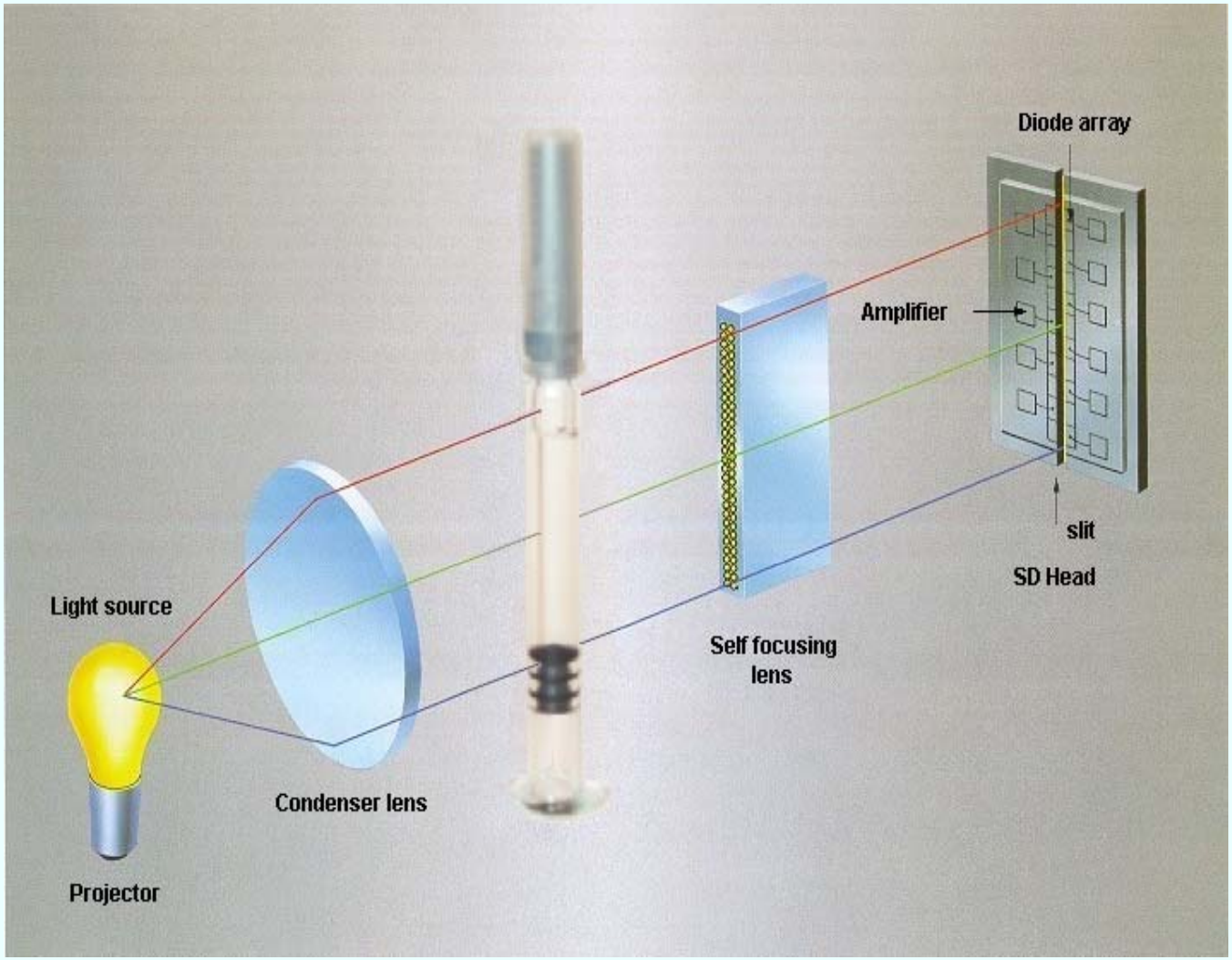
Closed Loop Validation

Example

1. **Cap/Crimp Defects**
2. **Cracks in Body**
3. **Cracks in Bottom**
4. **Particulate Matter**



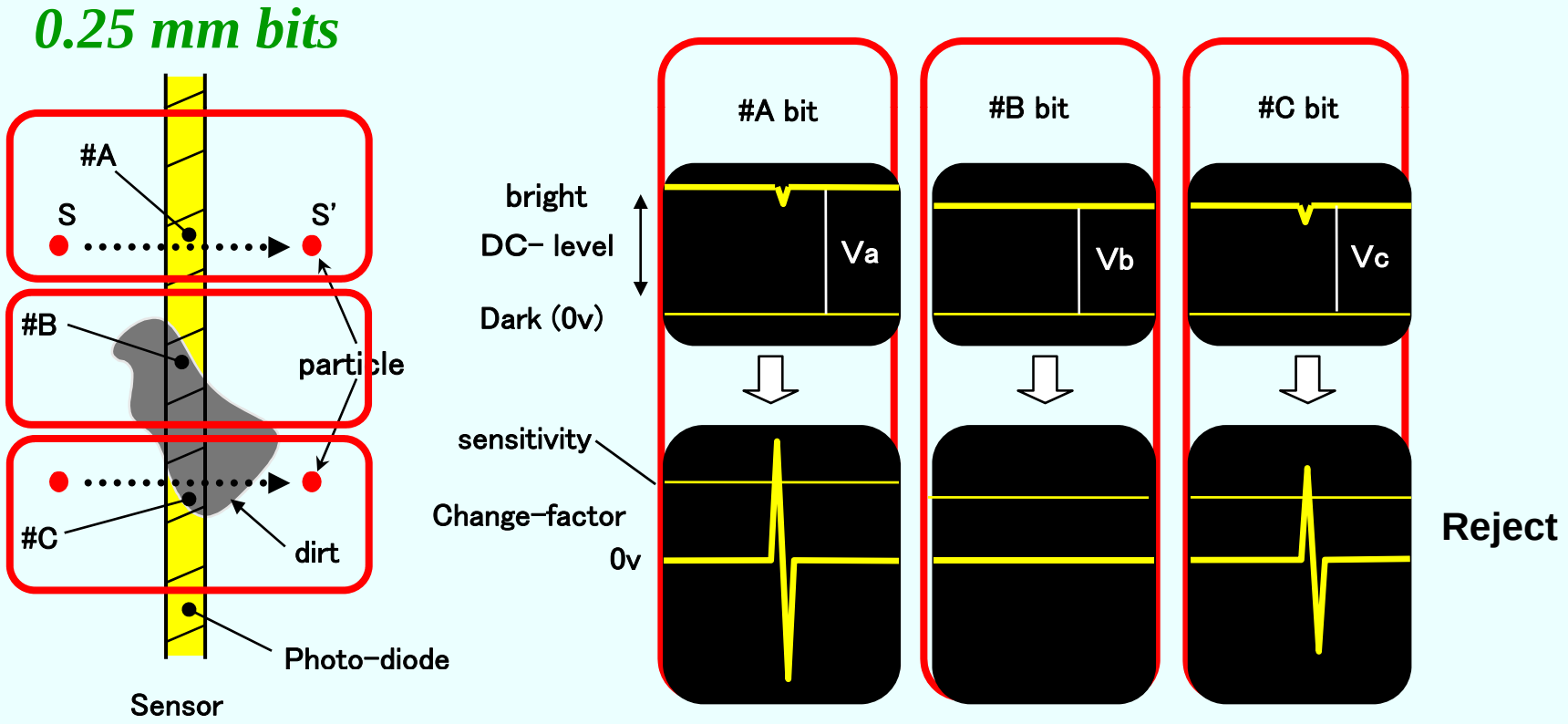
Programmable eject trays



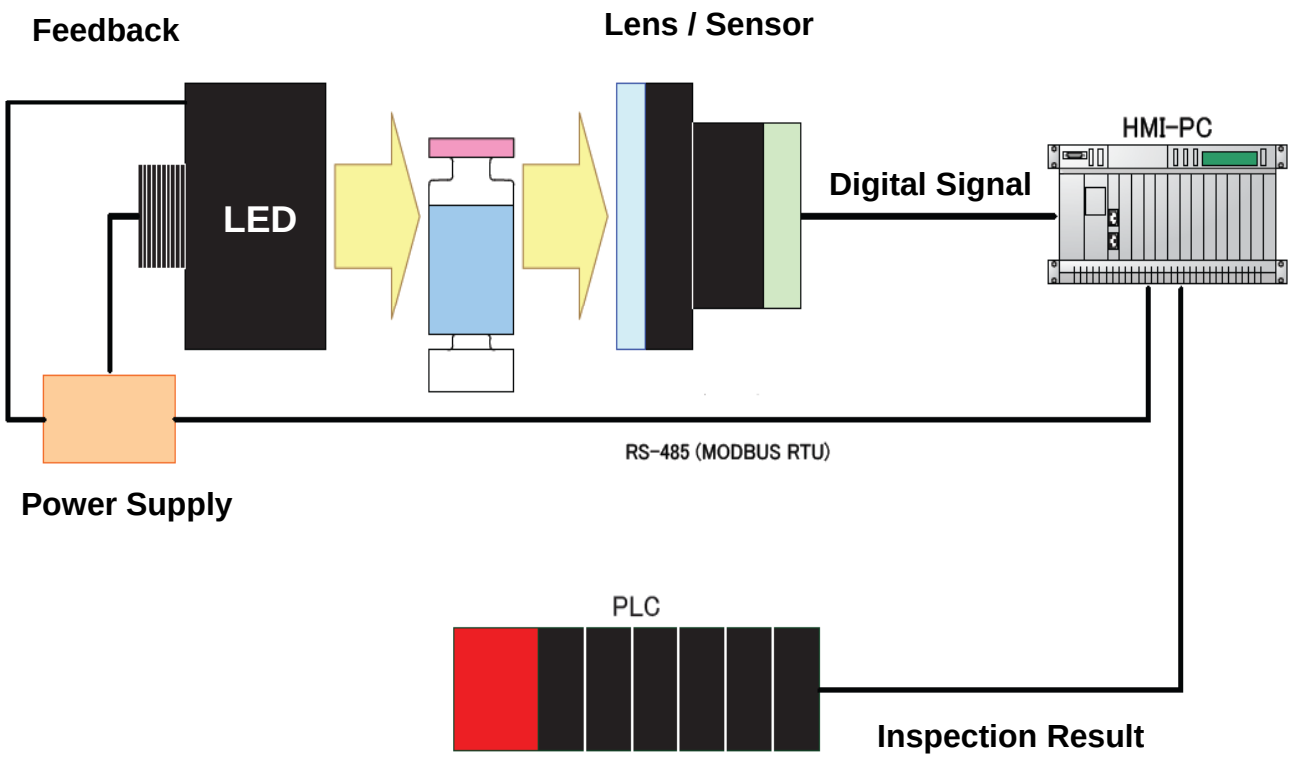
SD System - Particle Inspection

New-LED lighting method

Static Division - divides stationary shadows from moving particles.

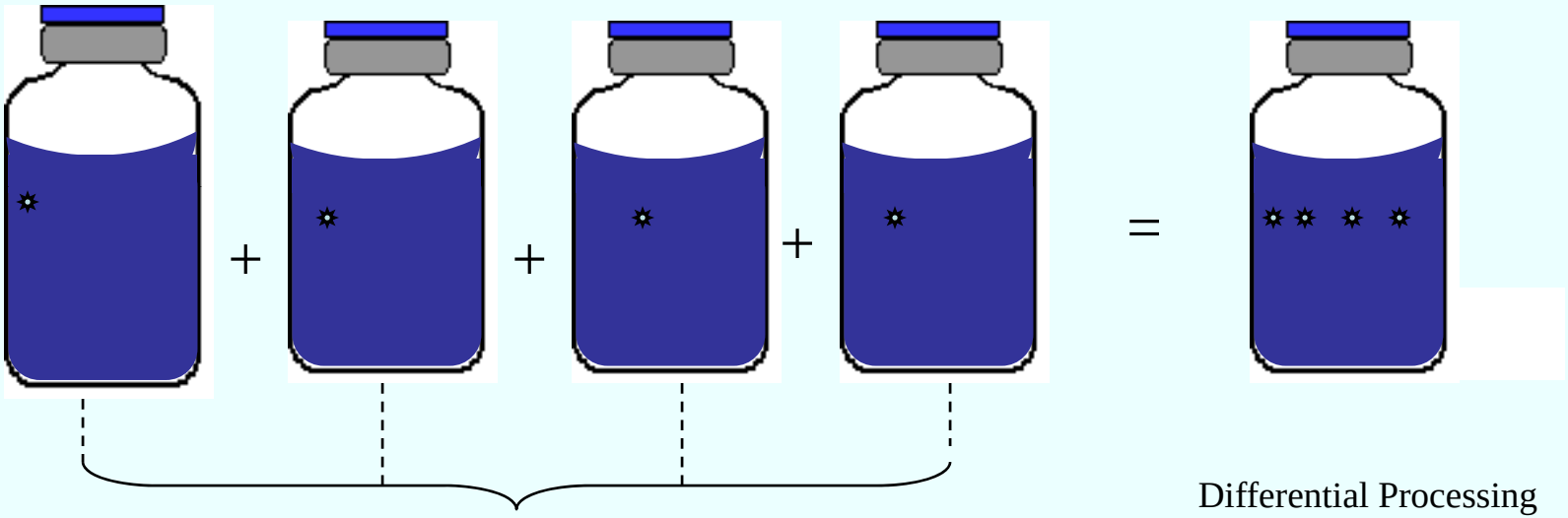


SDx Real Time Inspection system with smaller bits

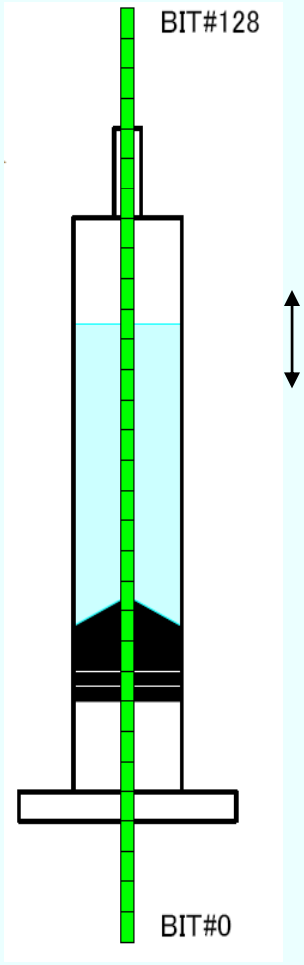


LED = Light emitting diode

CCD Camera – Charged Coupled Device

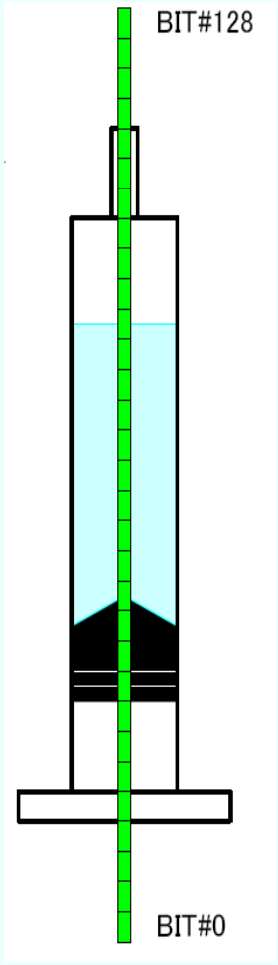


Particle Inspection by Camera System



Motion canceling capability

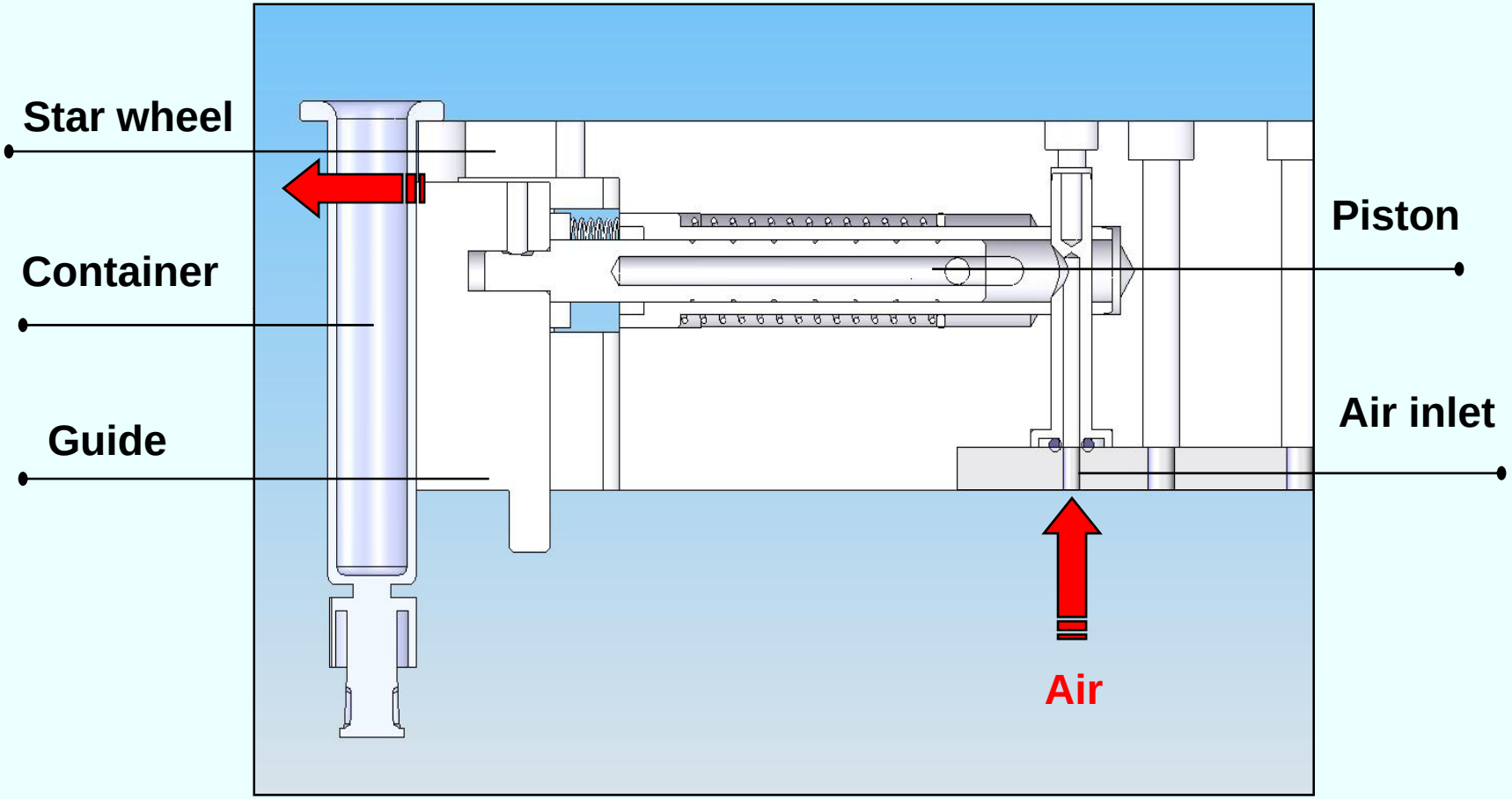
Meniscus



Inspection view area will change automatically based upon the position of the stopper

Body

Syringe Handling System without Vacuum



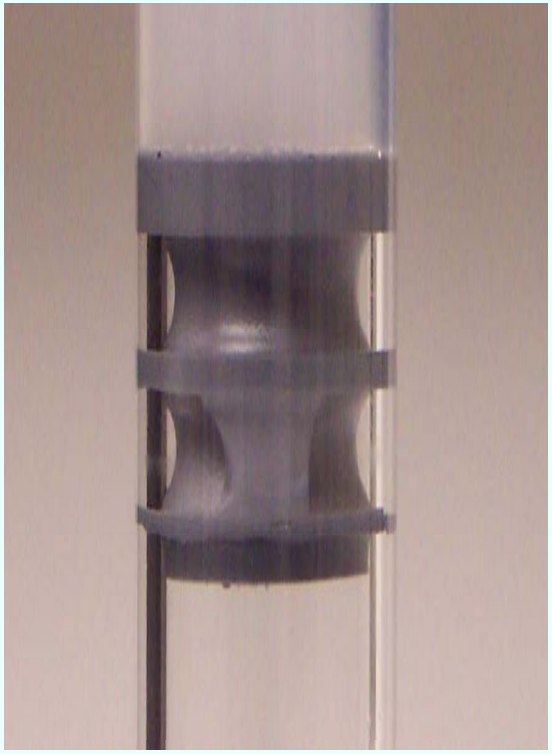
No Vacuum

Cosmetic Inspection

Typical (or common) Defects in Pre-Filled Syringes

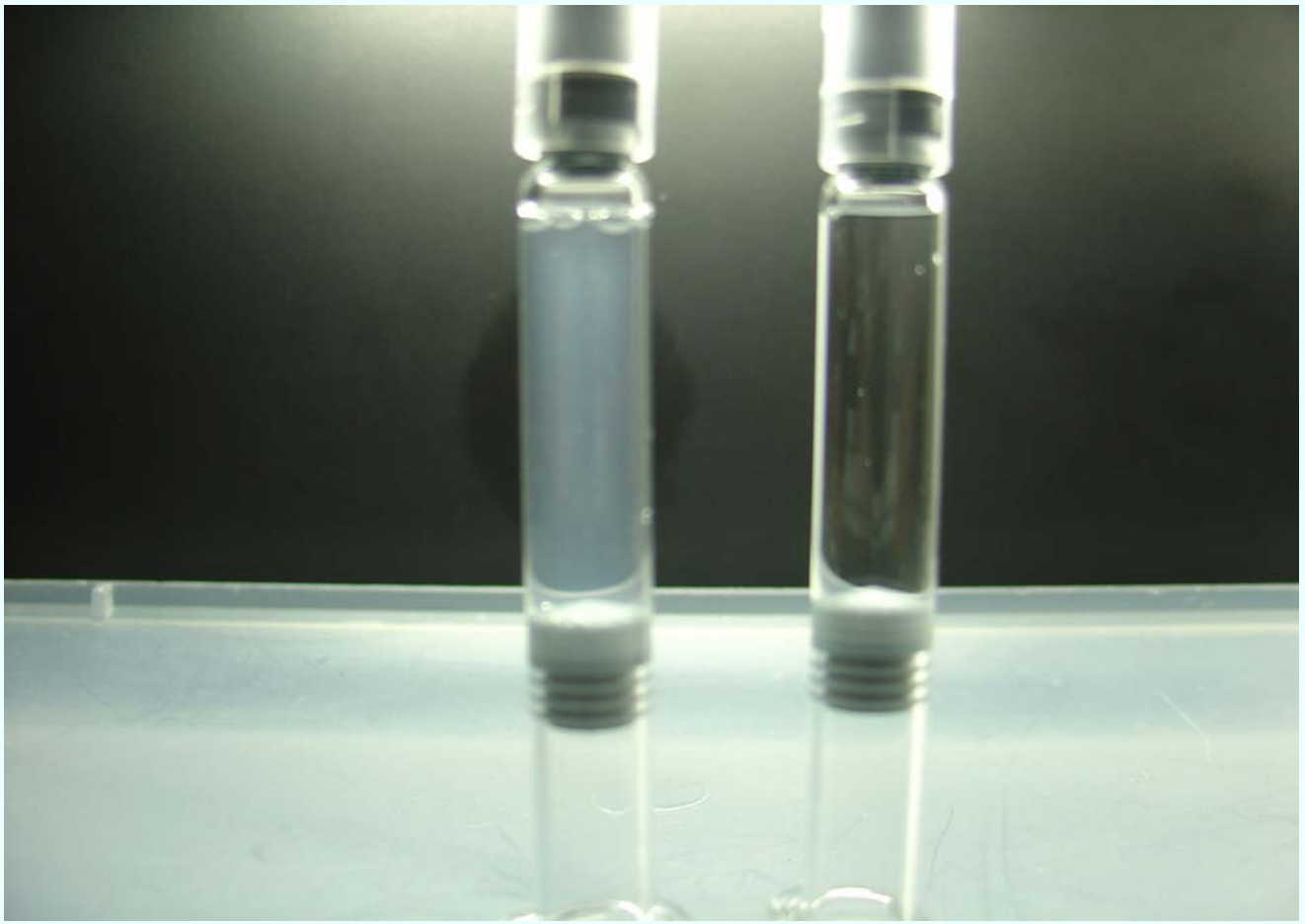
Cracks

Liquid in Ribs

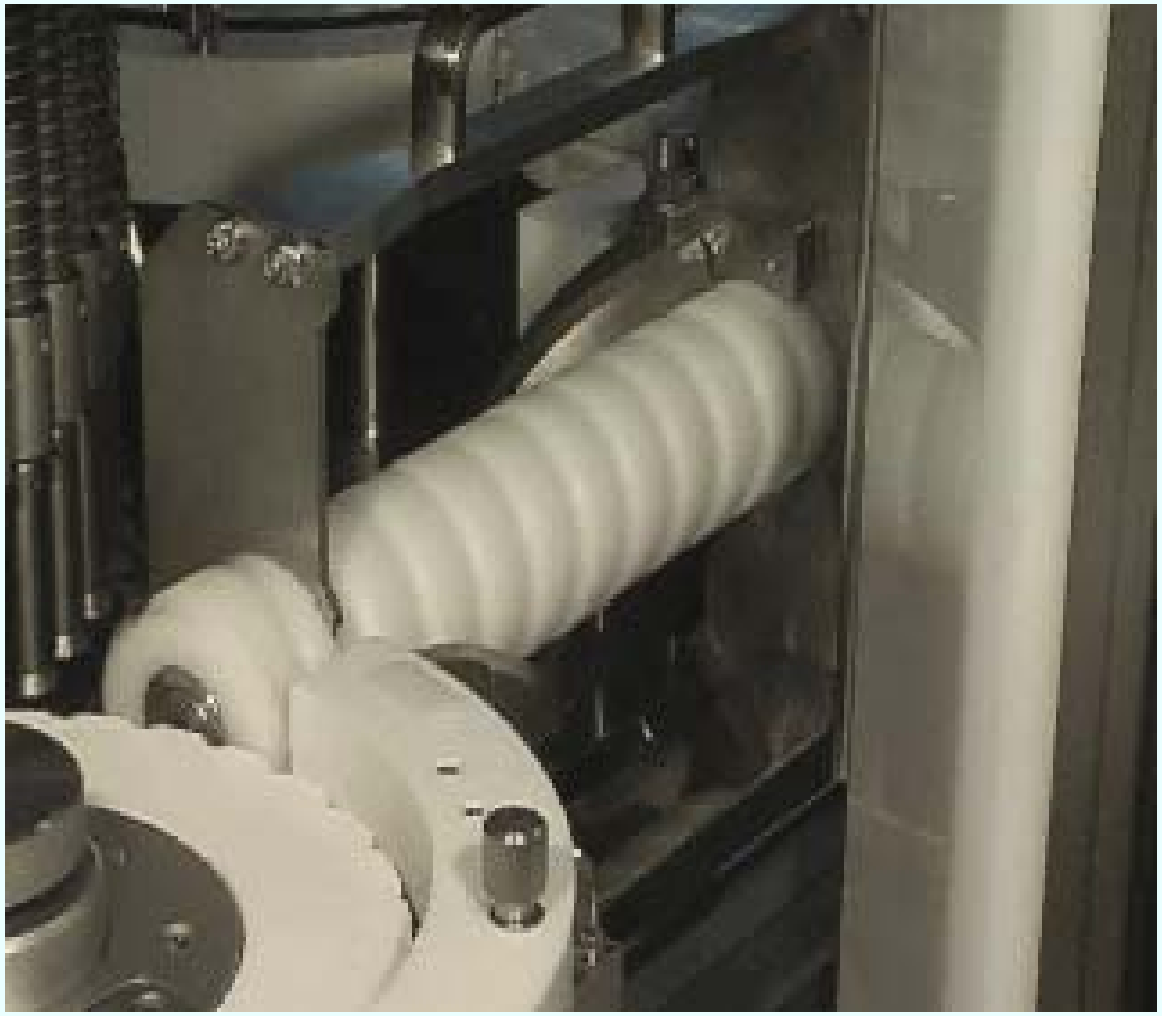


Inverted Stopper

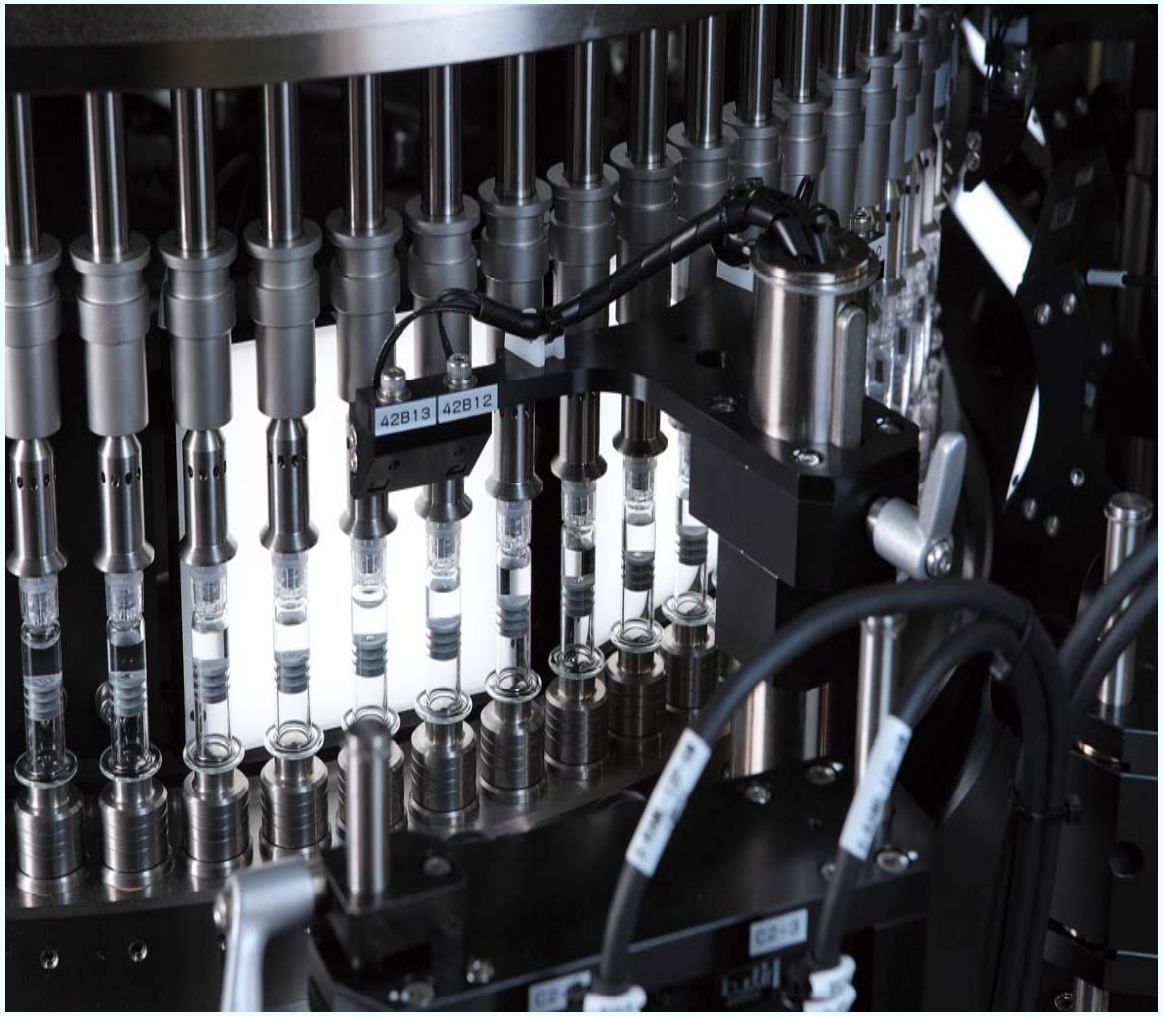
TURBID Solution … A Defect? What Level??



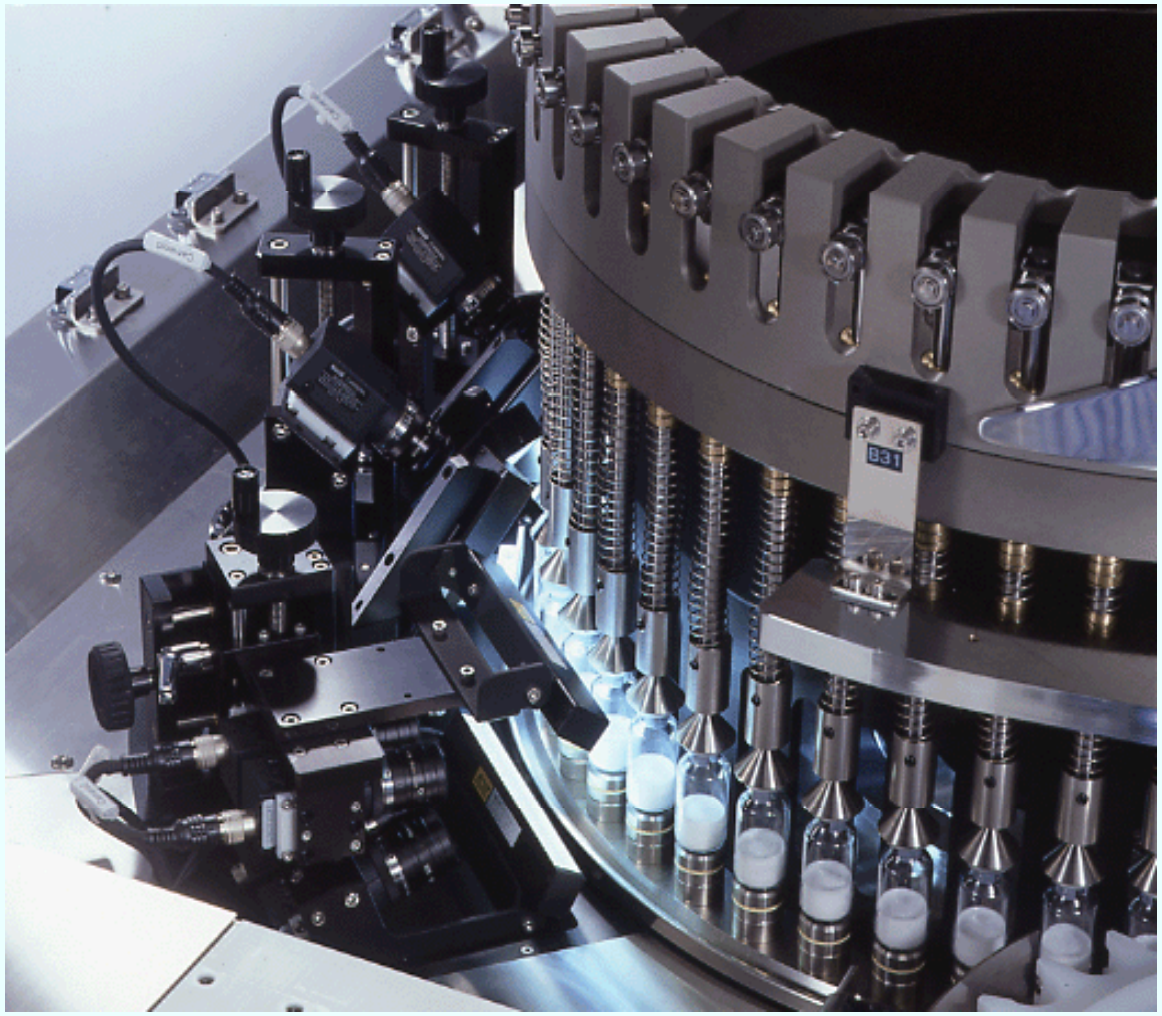
Container Handling



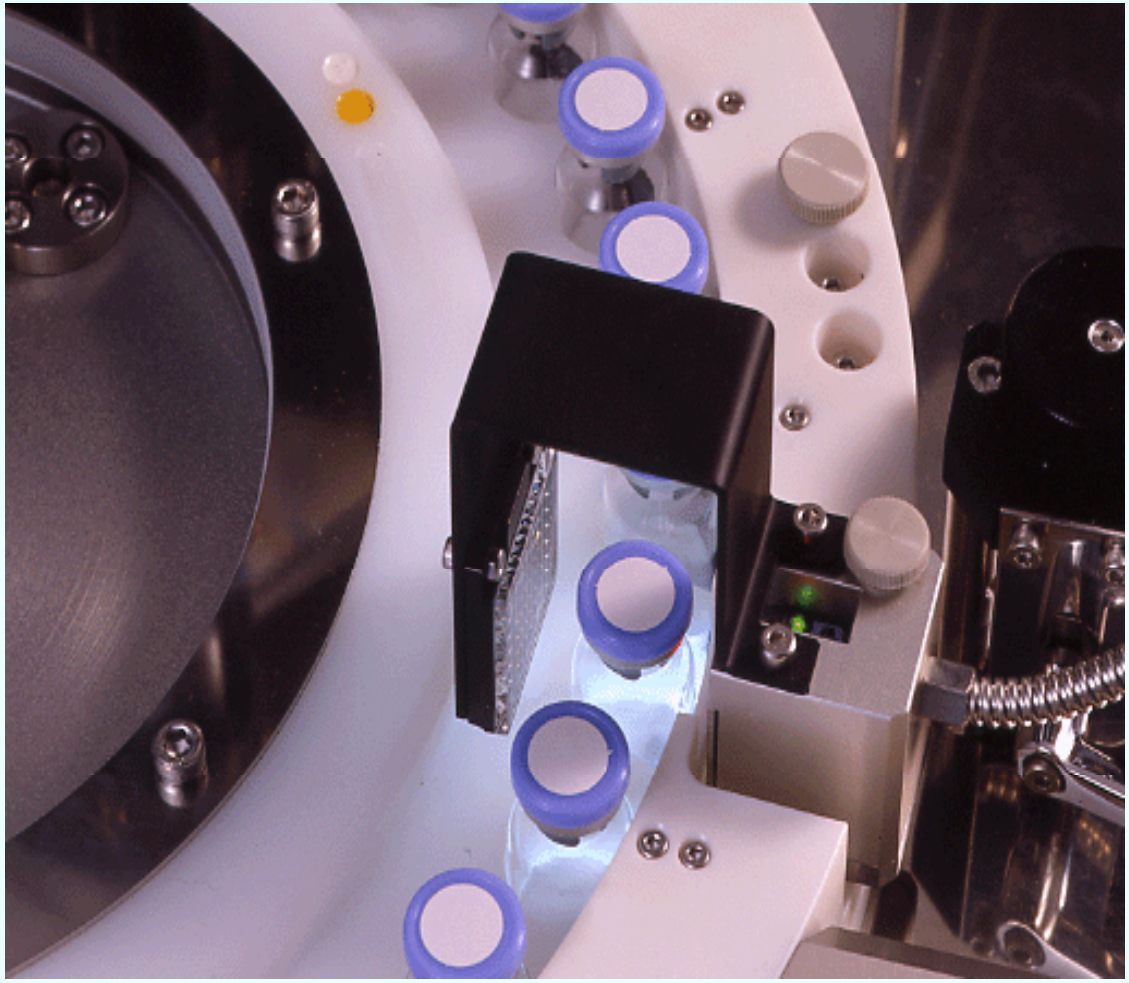
Inverting the Syringe



LED Lighting used for Cosmetic Inspection

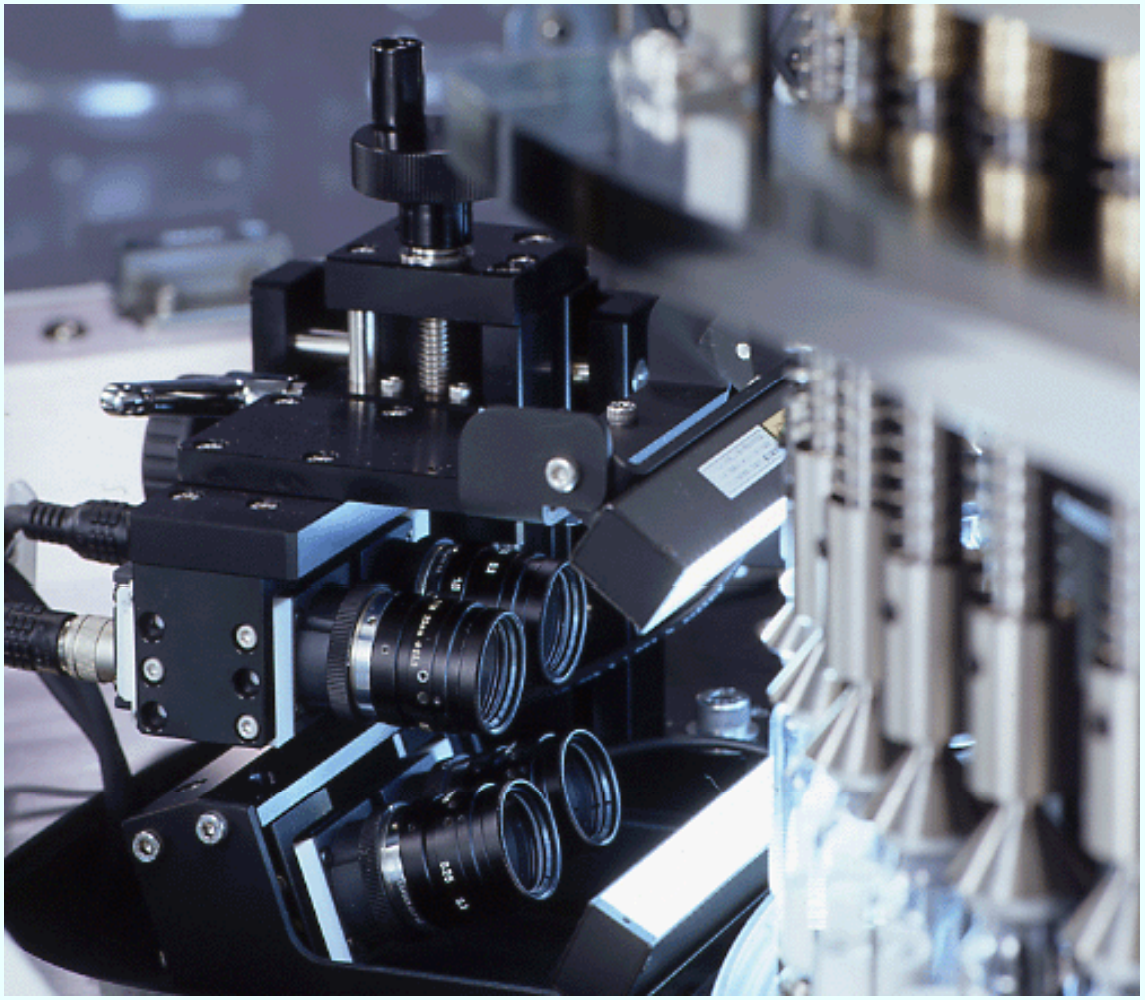


Lyophilized Product Inspection



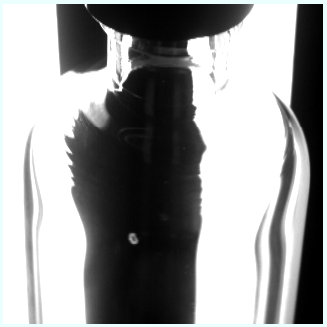
Cap & Crimp Inspection

Segregating Cake defects, Glass cracks, Melt back



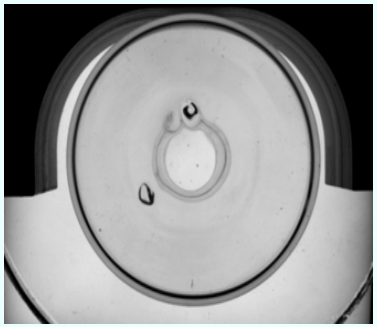
Empty Vial Inspection

Body Cracks



Shoulder Bruise

Heel Corner



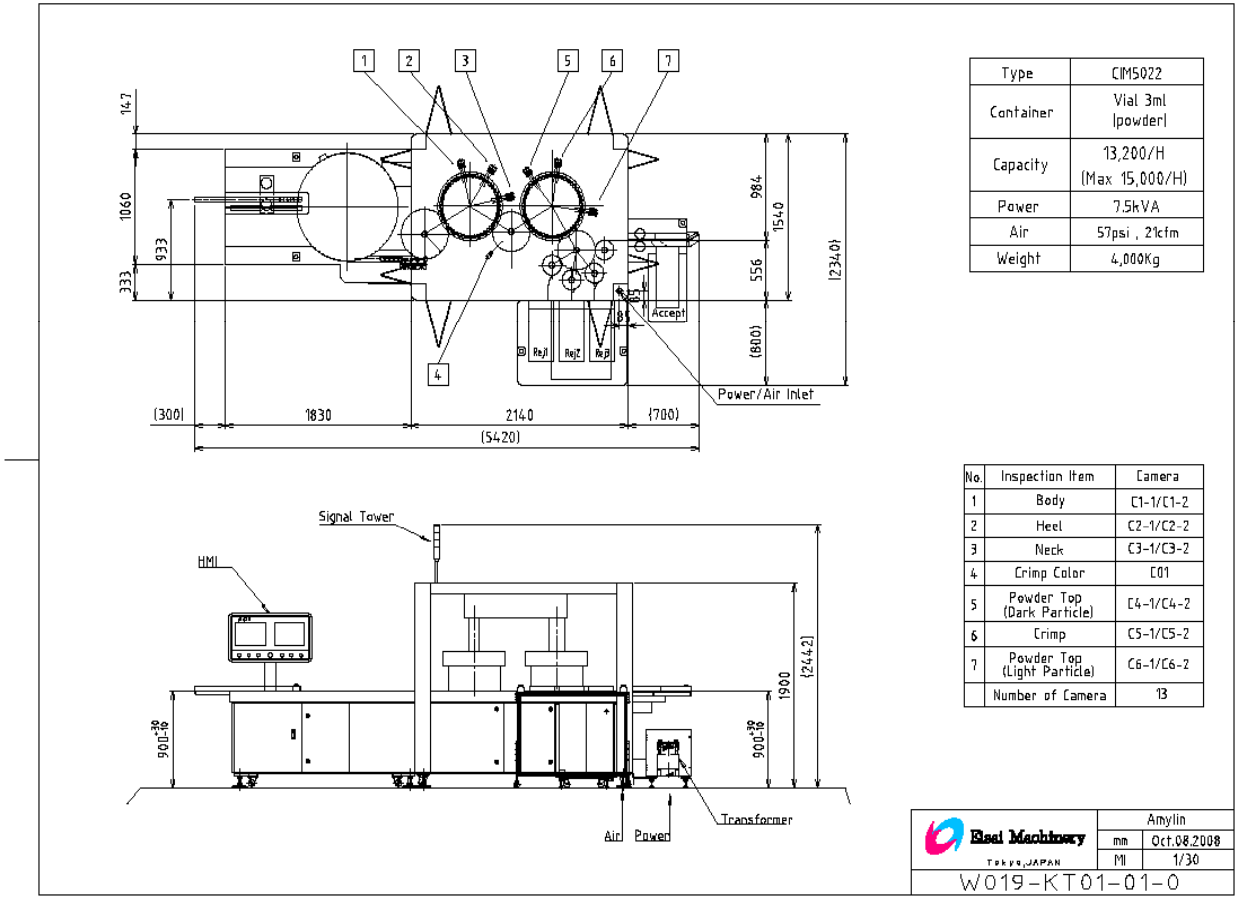
Bottom Cracks

Top Lip

Side Lip

Slant Lip

Empty Glass Defects

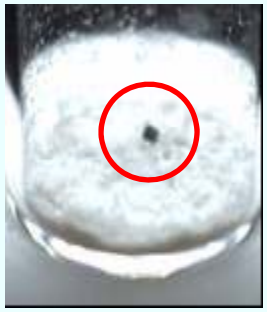


Type	CIM5022
Container	Vial 3ml (powder)
Capacity	13,200/H (Max 15,000/H)
Power	7.5kVA
Air	57psi , 21cfm
Weight	4,000Kg

No.	Inspection Item	Camera
1	Body	C1-1/C1-2
2	Heel	C2-1/C2-2
3	Neck	C3-1/C3-2
4	Crimp Color	C01
5	Powder Top (Dark Particle)	C4-1/C4-2
6	Crimp	C5-1/C5-2
7	Powder Top (Light Particle)	C6-1/C6-2
	Number of Camera	13

Powder Inspection – Machine Layout

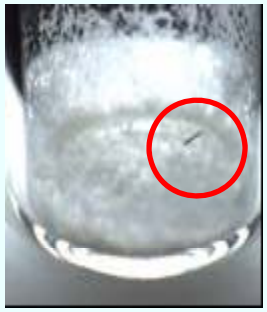
Stainless Ball



Stopper

Viton Gasket

Aluminum



Black Hair

Glass piece

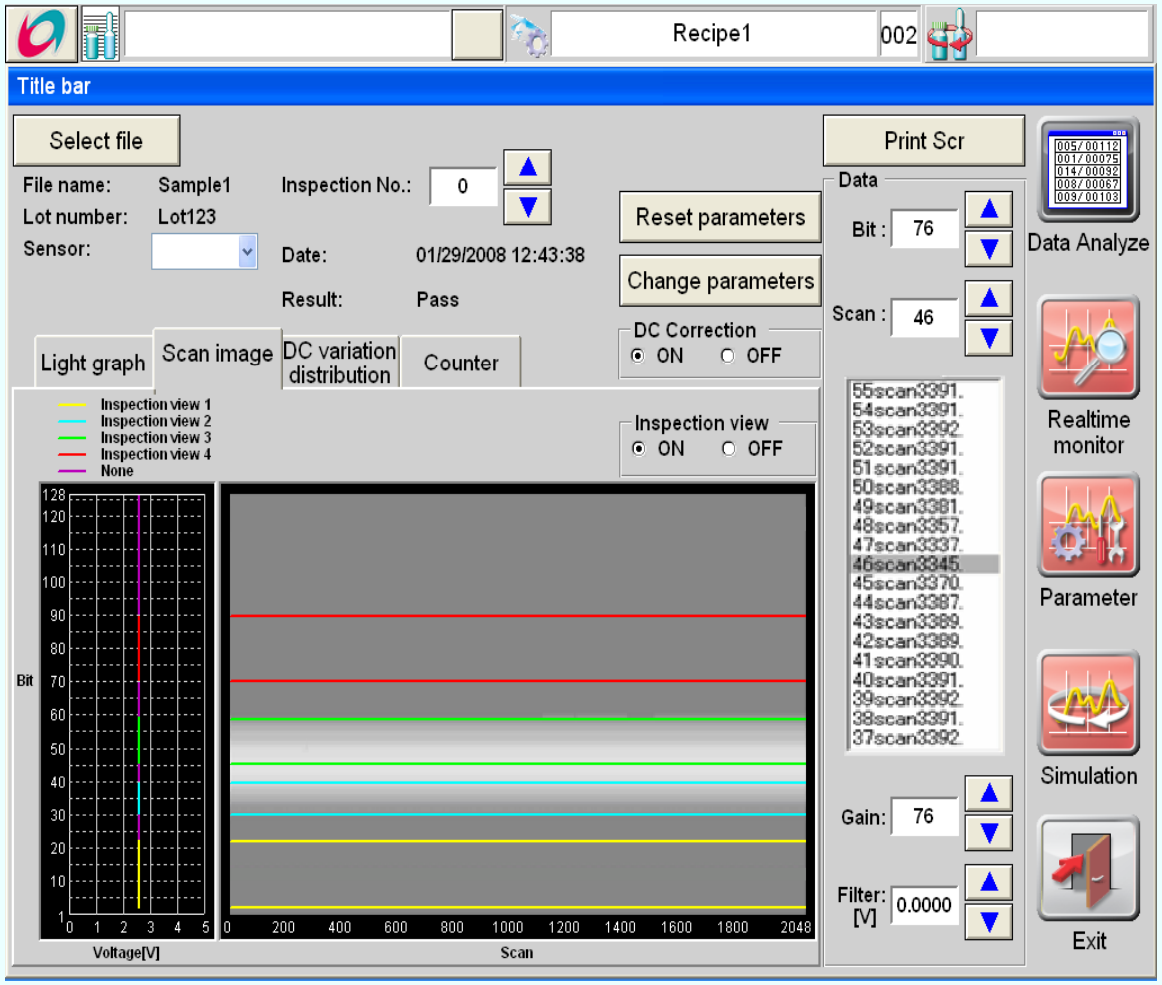
Accept

Accept

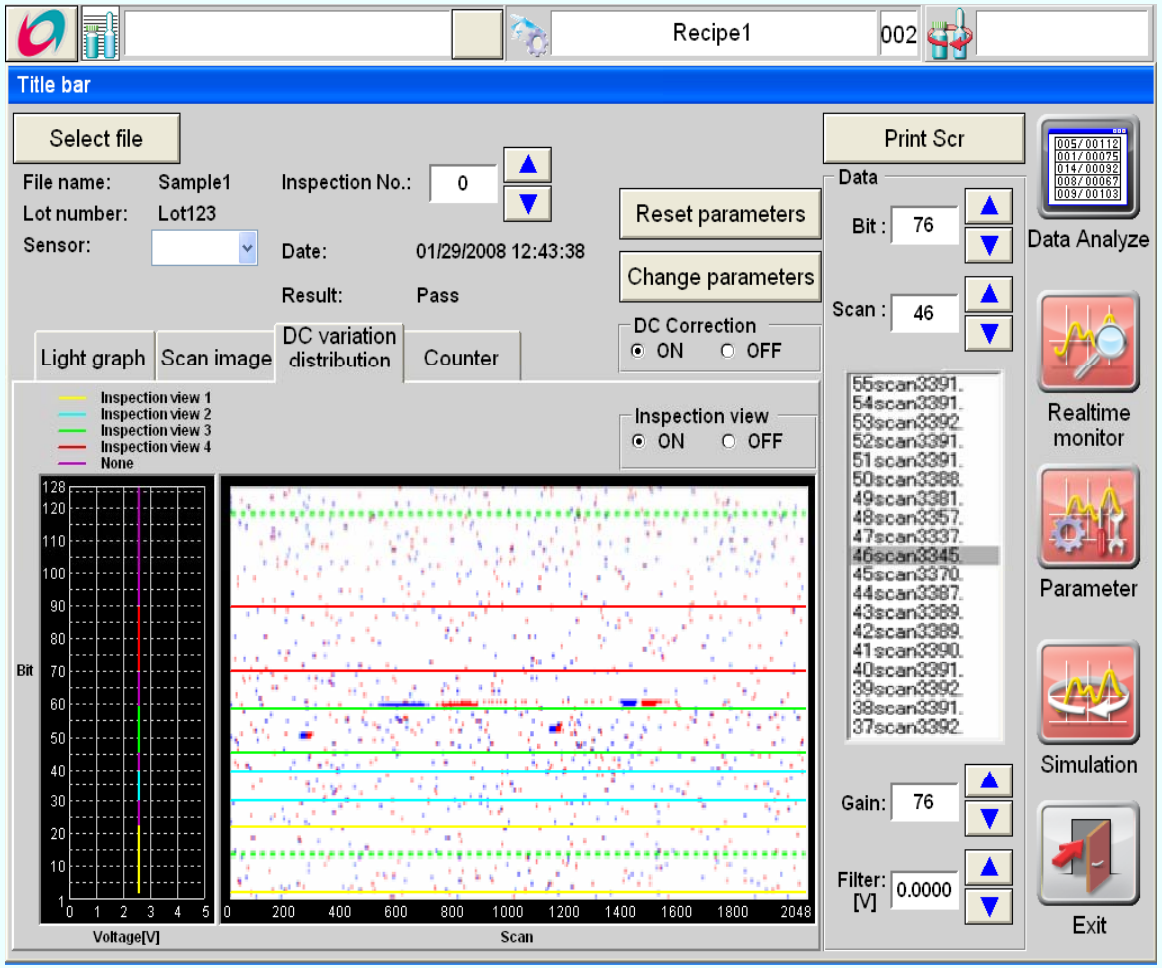
Powder Inspection

- Store images for off-line tuning and to view production conditions
- Save Failed images for helping troubleshoot False rejects
- Keep Record of up to 1,000 stored images

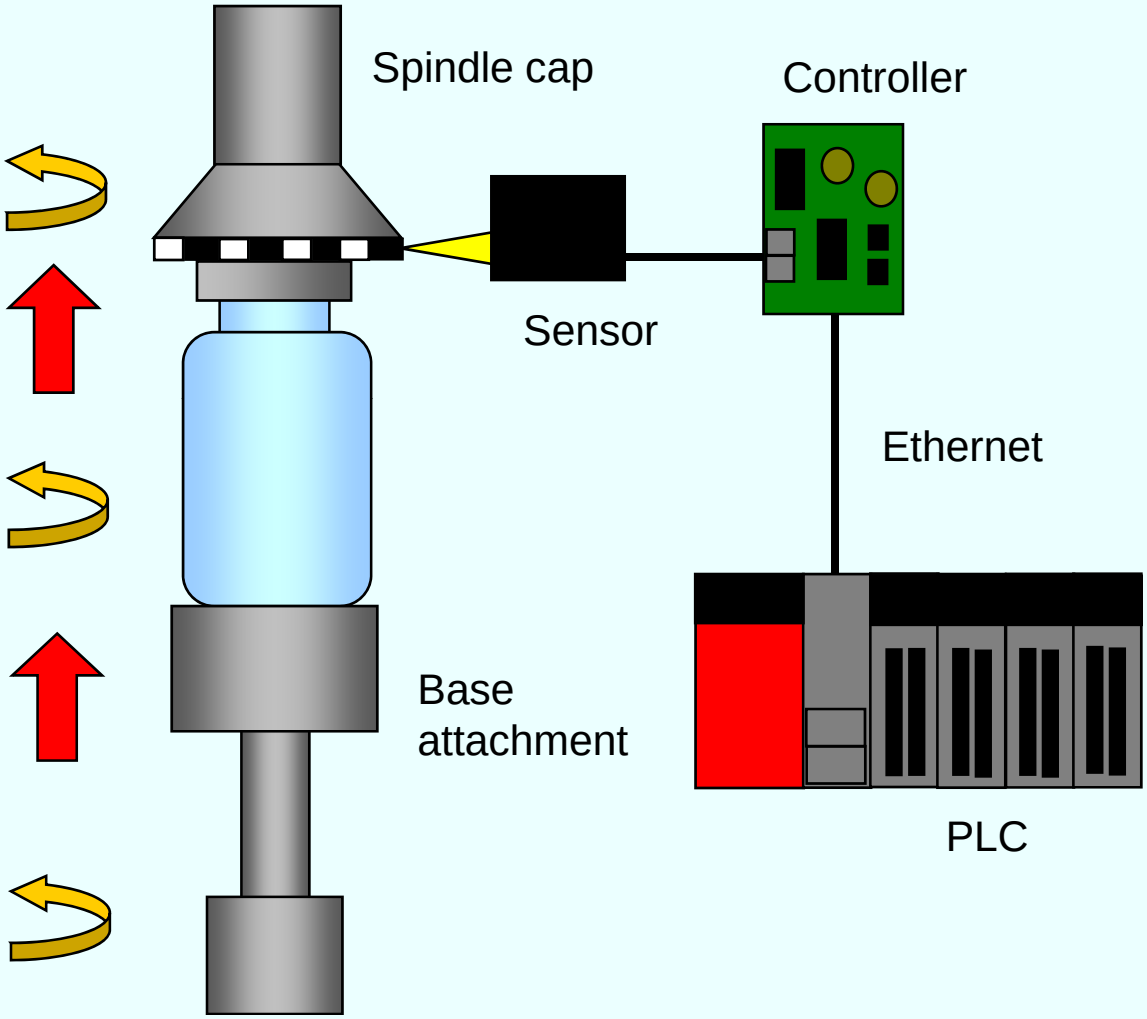
Regressive Testing



Scan Images for Off-Line Tuning

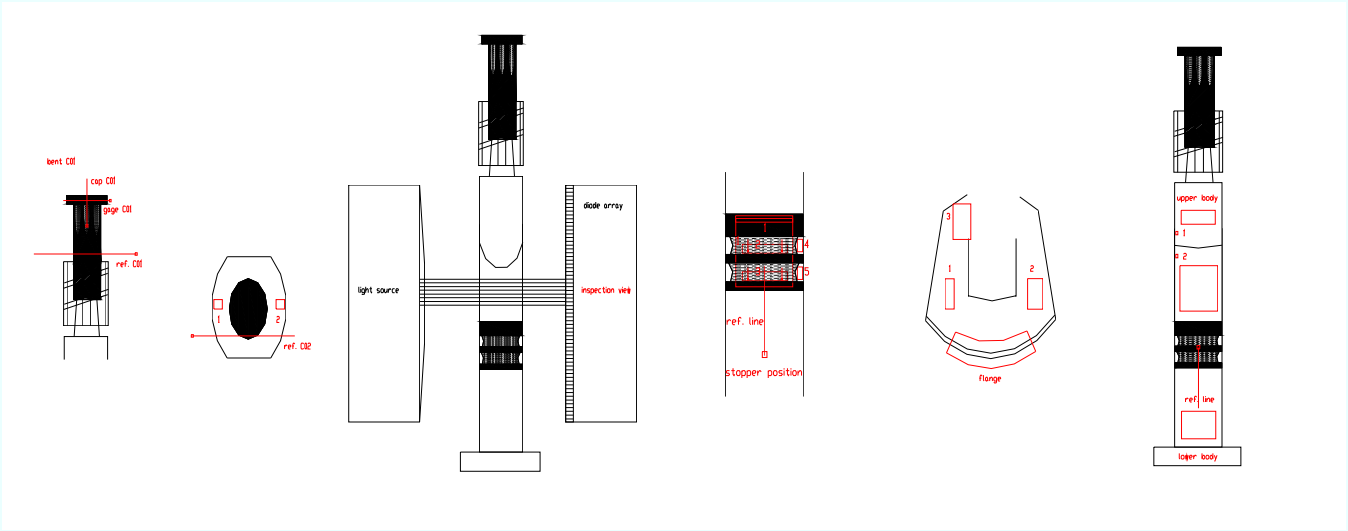

Recipe1
002
Title bar
Select file
File name: Sample1
Lot number: Lot123
Sensor:
Inspection No.: 0
Date: 01/29/2008 12:43:38
Result: Pass
Reset parameters
Change parameters
Print Scr
Data
Bit : 76
Scan : 46
DC Correction
ON OFF
Light graph
Scan image
DC variation distribution
Counter
Inspection view 1
Inspection view 2
Inspection view 3
Inspection view 4
None
Inspection view
ON OFF
55scan3391.
54scan3391.
53scan3392.
52scan3391.
51scan3391.
50scan3388.
49scan3381.
48scan3357.
47scan3337.
46scan3345.
45scan3370.
44scan3387.
43scan3389.
42scan3389.
41scan3390.
40scan3391.
39scan3392.
38scan3391.
37scan3392.
Bit
Voltage[V]
Scan
Gain: 76
Filter: [V] 0.0000
Data Analyze
Realtime monitor
Parameter
Simulation
Exit

Spin Verification System



Spin Speed Verification

The Eisai Inspection System is configured to inspect containers utilizing Static Division “SD” sensors for particulate matter defects, and a series of high-speed vision processors for inspecting cosmetic defects on the needle, flange, stopper, barrel, and checking fill level.



Inspection Tool Parameters

After execution of IQ and OQ, a series of Developmental Studies are conducted to establish the inspection tools and the challenge set containers that would be utilized for performance qualification.

A Knapp Study is conducted in order to develop inspection tools that will provide evidence that the inspection of rejects on the Eisai machine (classified by manual inspection) are equivalent or superior to manual inspection.

Three (3) groups of 200 containers each were subjected to manual inspection (50 total inspections).

Additionally, false rejection of containers is evaluated in an effort to minimize the false reject rate and optimizing the rejection rate.

Creation of challenge set defect containers (with actual defects located in each inspection area) along with the associated rejection rates for each defect group, that would be utilized for process validation and production operations.

Containers are segregated into three (3) main categories for each defect inspection station:

- critical (directly impacts the product)
- major (affects the usability of the container)
- minor (does not impact product or container)

As a result of the study, each defect inspection station challenge set had a minimum detection percentage that would be applied to the production challenge set.

Development of the SD inspection station settings utilized six types of particulate matter defects, (SS, glass, hair, tyvek, skin, stopper) each with four size ranges: (100-300, 400-500, 600-800, ≥900 microns)

Four (4) different sensitivities were tested, and the sensitivity setting with the optimal rejection and false rejection rates was selected.

After completion of development studies and establishing standard operating procedures including production batch records, a *Performance Qualification* was executed.

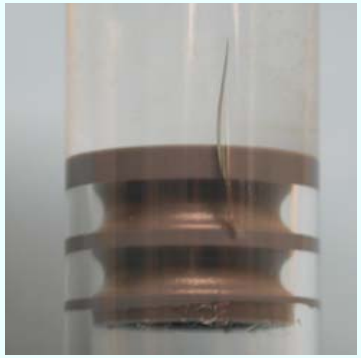
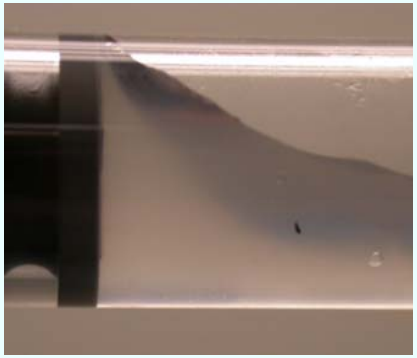
Three (3) lots were processed through the Eisai inspection line and an AQL analysis for critical, major and minor defects was completed to ensure that the Eisai system was capable of continuously inspecting containers for defects to meet the pre-determined quality levels.

The creation and maintenance of the challenge set samples is critical to ensure that the inspection machine is maintaining the validated state under dynamic conditions (i.e. lamp intensity, vision or particulate system conditions) and also provide a basis for adjustment of inspection parameters while maintaining the validated state.

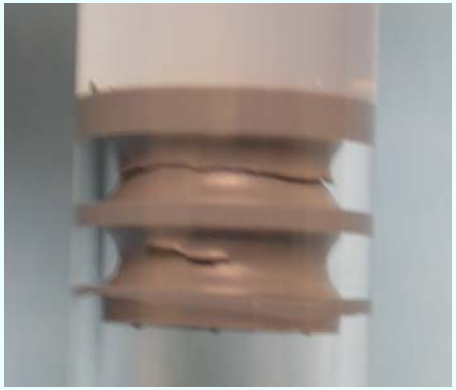
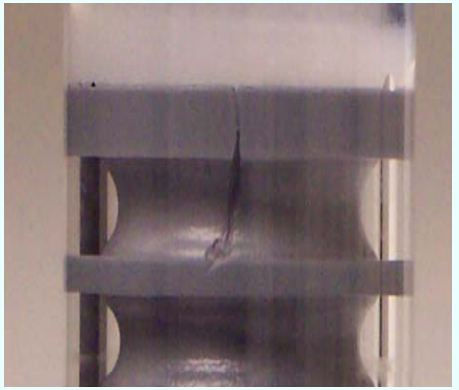
Each challenge set container should be an actual defect encountered from the process. If an actual defect has not been encountered, then a defect may be created manually. (i.e. chipped/cracked flange).

A challenge set procedure (based on the results of the qualification studies) needs to be defined that will allow for replacement containers for the challenge set when a challenge set container is placed out of service. (i.e. due to breakage)

There needs to be a container with a defect in each of the qualified inspected areas of the container.



Challenge Set Samples

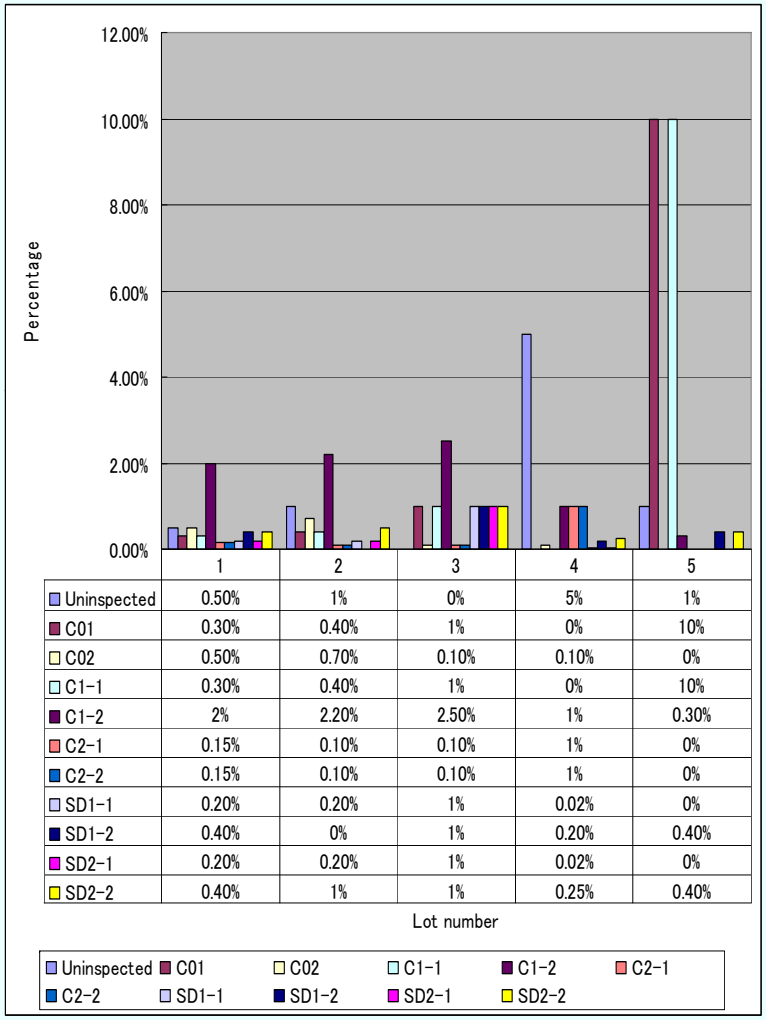
Added functions to Eisai's standard APK inspection device helps make verifying defects and creating sample sets much easier.

APK – Visual Observation Tool

Establishing defect ratio percentage limits for each inspection station that will alert/alarm when exceeded, is an important step for real-time process evaluation and improvement to ensure the lot quality exceeds the established quality assurance limits.

		Ratios	Alarm Setpoints
116706	Total inspected		
1883	Total rejected	1.61 %	2.91 %
73	C01 Tip cap	0.06 %	0.13 %
2	C02 Broken Flange	0.002 %	0.01 %
663	SD Particle	0.57 %	1.15 %
543	C1 Stopper	0.47 %	1.07 %
31	C1 Stopper Position	0.03 %	0.21 %
61	C2 Flange	0.05 %	0.09 %
483	C3 Barrel	0.41 %	0.72 %
7	C3 Fill Level	0.006 %	0.02 %

Added report function provides overall reject percentages for each lot, per camera station.



	1	2	3	4	5
Uninspected	0.50%	1%	0%	5%	1%
C01	0.30%	0.40%	1%	0%	10%
C02	0.50%	0.70%	0.10%	0.10%	0%
C1-1	0.30%	0.40%	1%	0%	10%
C1-2	2%	2.20%	2.50%	1%	0.30%
C2-1	0.15%	0.10%	0.10%	1%	0%
C2-2	0.15%	0.10%	0.10%	1%	0%
SD1-1	0.20%	0.20%	1%	0.02%	0%
SD1-2	0.40%	0%	1%	0.20%	0.40%
SD2-1	0.20%	0.20%	1%	0.02%	0%
SD2-2	0.40%	1%	1%	0.25%	0.40%

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