Development of KWS9001AP10/20/30 Capsule Checkweigher

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[Summary] We have developed a new capsule checkweigher featuring validation functions assisting customer GMP activities as well as high-accuracy measurements of ±0.5 mg. To implement high-accuracy measurement, instead of using the differential transformer method from earlier models, we developed a new miniature force balance method supporting sufficient accuracy for weight selection of empty capsules. The capsule carrying mechanism has also been separated completely from the mechanical section including the weighcell, helping reduce ingress of foreign materials. Moreover, we have designed tool-free disassembly and assembly when changing parts according to capsule number, simplifying cleaning and reducing the risk of product cross contamination.

1 Introduction

Anritsu has been a world leader in development and release of checkweighers since 1970. Our products are not only used domestically in Japan but are also used by many pharmaceutical manufacturers overseas. Subsequently, in line with ideas about Good Manufacturing Practice (GMP) related to manufacturing and product quality management, validation of manufacturing processes and facilities started to become standardized. In 1997, in addition to achieving the maximum throughput of 120,000 products per hour and the maximum accuracy of ±2 mg, we also developed and released the third-generation KW9001AP supporting various validation actions. This checkweigher was popular not only in Europe and America but also made inroads into NIEs producing generic pharmaceuticals, such as India, Puerto Rico, etc.

On the other hand, recently, there is increasing world awareness about the usefulness of quality assurance systems based on GMP standards. Consequently, national governments and inspection organizations have been working on compatibility to assure the PIC/S GMP standards can be adopted worldwide. However, recently there has been an increase in lack of data integrity as a specified inspection item. Consequently, there is a need for data management systems (electronic records and electronic signatures) typified by the FDA 21CFR Part11 regulation.

Previously, the raw materials used by pharmaceutical capsules included gelatin made from animal extracts such as beef bones, pig skin, and fish products. However, as a result of the BSE problem and to cope with religious belief issues and demands of users, various new capsule raw materials using pulp-based Hydroxypropyl Methylcellulose (HPMC) and non-animal plant-based starches such as Pullulan have been developed. The previous animal extract gelatin capsules used well-established manufacturing processes yielding capsules with very low randomness in capsule mass. However, non-animal-based capsules are more difficult to manufacture, resulting in larger randomness in capsule mass. When necessary, capsules can be an essential part of a controlled-release drug delivery system (DDS), delivering the right amount of medication at the right location in the body. However, when the capsule has large randomness in mass, this DDS function may not work sufficiently well. As a result, stabilizing the quality of non-animal product capsules with large randomness in mass, requires weighing and selection of capsules before filling with the drug medication.

Moreover, anti-cancer drugs using antibody therapy, and immunosuppressants, both of which have high effectiveness at very low doses are now being developed as mainstream pharmaceuticals. Manufacturing of these types of the pharmaceuticals which are expected to become more commonplace in the future requires even more severe management of mass by weighing and selection prior to capsule filling as well as overall high accuracy inspection after filling.

Figure 1 External View of KWS9001AP20 Capsule Checkweigher

To meet these diverse requirements, we have developed the fourth-generation KWS9001AP series Capsule Checkweigher (Figure 1). This product is designed for high accuracy rejection of capsules before filling as well as for capsules filled with high pharmacological activity drugs, both of which were difficult to achieve using previous checkweigher models. Additionally, this series also supports data quality management functions with tamper-free recording of inspection results and built-in restricted-access functions. This article outlines the new KWS9001AP series.

2 Development Concept

Meeting market needs required solving the following three important issues.

(1) Faster Speed and Higher Accuracy
- Improve from previous checkweigher throughput of 60,000 products/h to 75,000 products/h while maintaining same or smaller footprint
- Support larger capsules with higher measurement accuracy by improving previous weight range from 1000 mg to 2000 mg and scale interval from 0.5 mg to 0.1 mg
- Reduce effect of external factors such as temperature change and vibration to achieve maximum accuracy of ±0.5 mg

(2) Improved Reliability and Prevention of Product Cross Contamination
- Carrying empty lightweight capsules with stability and no reduction in center of gravity
- Prevent foreign matter adhering to capsules and product cross contamination
- To shorten production time when switching between different products, implement parts exchange without special tools and prevent reassembly mistakes
- improve reliability of statistical data and prevent mixture of overweight capsules with correct weight capsules
- implement self-diagnostic and operation check functions to simplify confirmation of checkweigher status

(3) Improved Operability and Support for FDA 21 CFR Part11
- increase size of operations screens and improve monitoring and operability
- Save and display user authentication and mass-production data and implement output data encryption to support FDA 21 CFR Part11

3 Development Points and Implementation Procedure

3.1 Development of New Force Balance Weighing Mechanism

The Anritsu-developed differential transformer weighcell used by previous products, which was damped using silicon oil, was based on the principle of converting the displacement of the spring weighing mechanism to an electrical signal using a differential transformer. However, this method requires periodic maintenance due to accumulated errors caused by degradation of the oil and micro-external forces. However, the force balance method used by this fourth-generation checkweigher uses a position detection sensor and electromagnetic force as a force balance at the position of the mechanical balance mechanism. The mass is found from the size of the current in the force coil required to achieve balance. Figure 2 shows the weighcell structure. The weigh table is coupled to a Roberval mechanism to reduce the mass measurement error due to load position. The load on the weigh table is transferred to the displacement magnification mechanism constructed using an elastic fulcrum. The magnified displacement is detected by the position sensor and the force coil current is controlled to bring

the balance mechanism back to the balanced state. This force coil current is converted to mass to yield the measured product weight.

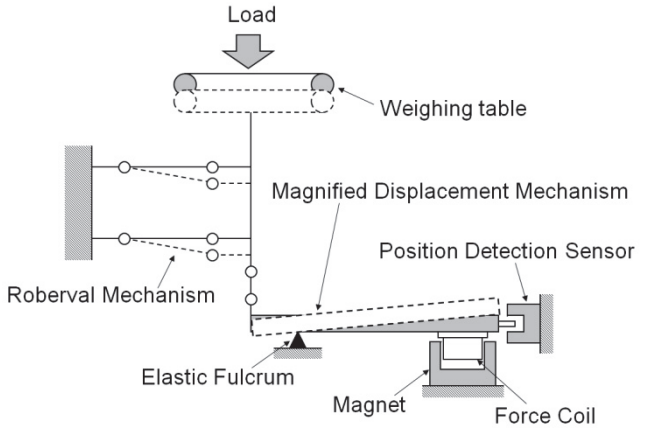

Figure 2 Force Balance Weighing Mechanism

The following equation shows how weight (mass) is determined.

$$F = BIL = \frac{Wg}{n}$$

$$W = \frac{nBIL}{g}$$

where, W is mass in kg, g is acceleration due to gravity in m/s^2, F is coil generation force in Newtons, n is magnified displacement in times (×), B is magnetic induction in Tesla, I is the force coil current in Amps, and L is the force coil length in meters.

Since this method detects the balance mechanism displacement and performs tracking control using the force coil generation force, it has better responsivity and measures weight more accurately than the differential transformer method. In addition, the balance mechanism can be fine-adjusted in the unloaded state to achieve a mechanism that minimizes the impact of external vibrations. Figure 3 compares the impact of external vibration (acceleration) on accuracy between the former series and the new KWS9001AP10, showing that the latter is much less affected and achieves higher weight-selection accuracy.

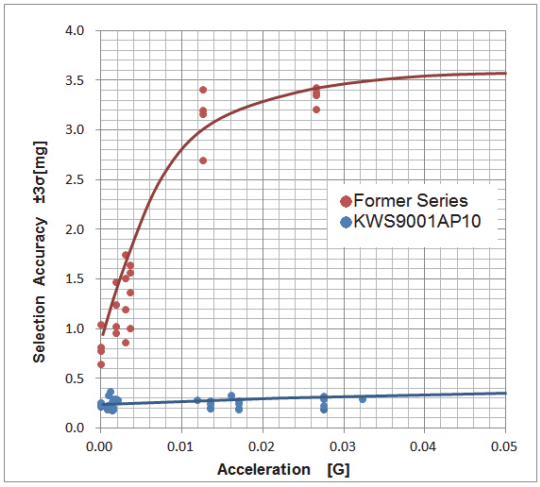

Figure 3 Effect of External Vibration on Accuracy

The main cause of damage to a weighcell in previous series is overloading due to pressure on the weighing table when changing parts and cleaning. As a result, the area around the weighing table has a protective structure to prevent contact. Additionally, to prevent a load exceeding the weight range, we have added a protective mechanism so that excess loads are not transferred to the weighcell.

3.2 Capsule Carrying Unit

Earlier models were arranged with the weighcell directly under the weighing table for weighing capsules. As a result, fine powder accumulated between the balance springs and stopper to degrade the accuracy. In addition, since rejection sorting was performed immediately after weighing was completed, it was difficult to assure sufficient space for the rejection operation. In this new series, to assure sufficient time until rejection, the weighcell is not positioned directly under the weighing table and weighcell arranged zigzag. This stabilizes accuracy, improves rejection reliability, and reduces space by weighcell installing with spacing of 20-mm, enabling a smaller installation space than earlier models and permitting 10 lines to be installed in the same space as occupied by 8 lines using the previous model, which achieved a improvement throughput. In addition, separation of the drive motors and mechanisms etc., from the capsule Carrying area prevents contamination of capsules with foreign materials, such as dust and oil. Moreover, stabilizing carrying of unfilled capsules favors better carrying of filled capsules, improved throughput and higher accuracy.

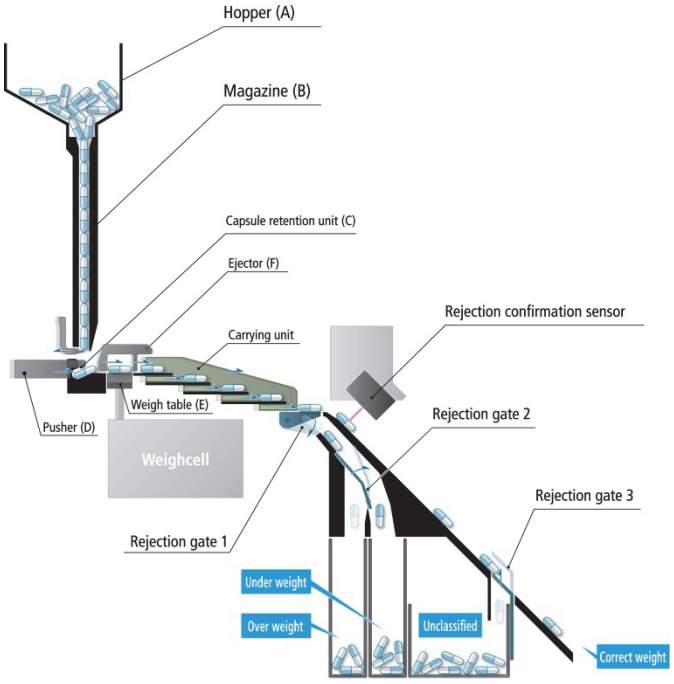

Figure 4 Capsule Carrying Path

As shown in Figure 4, capsules in the hopper (A) move single file into the magazine (B). To stabilize the flow of the unfilled capsule line, a shutter mechanism has been added to the magazine to help improve the carrying reliability. The aligned capsules move from the bottom of the magazine into the capsule retention unit (C) where each capsule is held for an instant before forcible horizontal alignment by the pusher (D) and insertion into the weighing table (E) where the weight is measured and the ejector (F) moves the weighed capsule to the next stage. The role of the ejector (F) is to prevent capsules flying out at movement to the carrying unit Weighed capsules are carried single file at a fixed interval on the v-shaped conveyor unit through rejection gate 1 that removes underweight and overweight capsules and passes correct-weight capsules. After correct-weight capsules have passed the rejection confirmation sensor they pass rejection gate 3 to exit the checkweigher. Overweight and underweight capsules are further separated into different boxes or exit chutes by rejection gate 2. Rejection gate 3 opens only to reject correct-weight capsules as a failsafe when the rejection confirmation sensor determines that a possible rejection error has occurred at rejection gate 1 or that the timing monitoring is out of specification.

3.3 Exchangeable Parts by Capsule Size

Like previous models, we have used a design supporting parts replacement matching capsule size to simplify cleaning parts coming into contact with capsules. As a result, this prevents accumulation of capsules and their contents in the checkweigher, and reduces the risk off product cross contamination when manufacturing various different products. Additionally, there is no need for special corresponding assembly and disassembly tools, offering tool-less service and shortening downtime to improve work efficiency. Moreover, installed parts are authenticated by a built-in size detection system using sensor verification, helping to prevent operation errors resulting from parts-installation errors. The magazine, pusher, capsule retention unit, and ejector shown in Figure 4 are all exchangeable parts. Finally, common parts such as the hopper, weighing table, carrying unit, rejection unit, etc., can all be removed without special tools to clean parts coming into contact with capsules.

3.4 Data Management Functions and Support for FDA 21CFR PART11

The main purpose of a capsule checkweigher is to accurately measure the weight of the target capsules and to reject overweight or underweight capsules not meeting the weight management reference value. In addition, statistical data collected on the measured weights and inspection values must be recorded as mass production results and for display on screens and for external output.

Previously, generally, printed statistical data was recorded and saved for use as quality management data. However, as standardized by FDA 21CFR Part11, in the future, actions and operations must now also be recorded as electronic data. Electronic data to be recorded not only includes statistical data for quality management but it also includes logs of actions and operations related to production as well as operation confirmation results before and after production as evidence of inspection conditions if required. Moreover, pre-recorded data on authorized users may be required to prevent falsification. This function can limit authorized users and also provides user-authentication management functions with all logs, results, and user records to be time stamped and recorded. These records make it possible to identify deviations from recommended operation procedures and to conduct fault analysis for improvements. This function also allows managers to preset user codes, passwords and access levels for each user to limit individual functions and operations, prevent unauthorized

log-ins, prevent failure to regularly update passwords, and provision automatic log-off, etc. Using these functions implements compliance with the requirements of FDA 21CFR Part11.

3.5 Improved Visibility and Operability

A large, high-visibility, 15-inch LCD touch panel has been added to the new KWS9001AP10 to help operators instantly understand the checkweigher status, the mass- production status, and the occurrence of any alarms and errors. Some typical operation screens are introduced below.

3.5.1 Zoom for Each Line Screen

The zoom for each line screen (Figure 5) displays product weights for a specific production line as an enlarged view as well as color-coded bar graphs for all lines to verify the machine status in real-time.

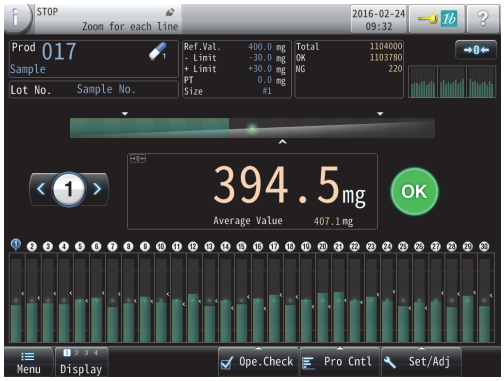

Figure 5 Zoom for Each Line Screen

3.5.2 Statistics Screen

The statistics screen (Figure 6) displays the various types of statistical data as histograms to confirm the mass-production status. The statistical data can also be switched between total and passed product counts.

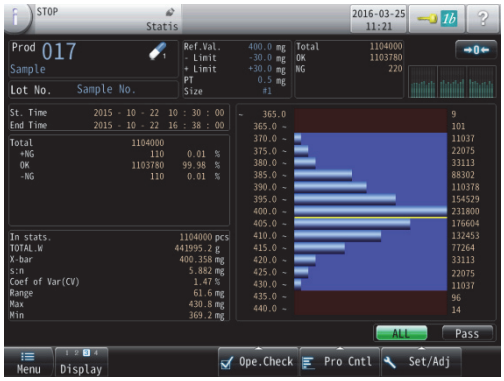

Figure 6 Statistics Screen

3.5.3 X-Bar · R/s Display Screen

The X-Bar · R/s display screen (Figure 7) displays mean values and standard deviations for each batch as a time series to help understand trends in measured products. The graphs can be switched between total and passed product counts for all production lines or each production line.

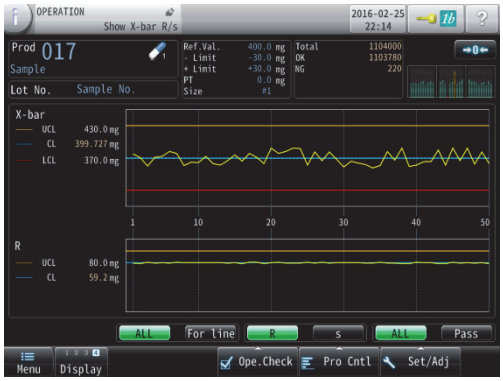

Figure 7 X-Bar · R/s Display Screen

3.5.4 Sensitivity Correction Screen

The sensitivity correction screen (Figure 8) is used by the administrator to simplify correction of the checkweigher by using conversation-response style answers to select weigh-cells requiring correction and inputting masses of master weights. Sensitivity correction is recorded and automatically for monitoring verification purposes.

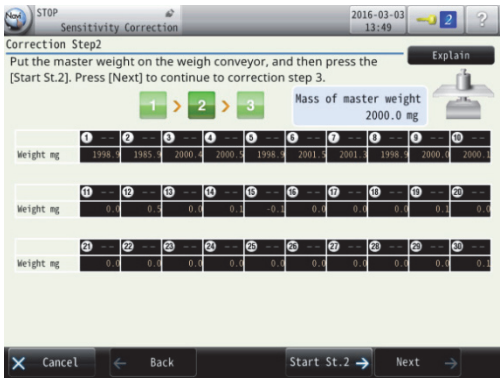

Figure 8 Sensitivity Screen

3.5.5 Daily Maintenance Screen

The daily maintenance screen (Figure 9) is used by the operator at the daily maintenance to check accuracy, rejection gate operation, and sensitivity based on conversation-response style answers.

The built-in auto sensitivity check procedure is completed automatically by one-button operation from the operation screen. As shown in Figure 10, after sensitivity correction using master weights, internal weights in the weighcell are weighed automatically and the results recorded to offer an indirect comparison between the master weights and internal weights for sensitivity check. At sensitivity check, the internal weights are weighed and the current measure-

ments are compared with recorded measurements and if there is any deviation it is verified as being within the permitted tolerance. Daily maintenance work is also recorded automatically for audit trail purposes.

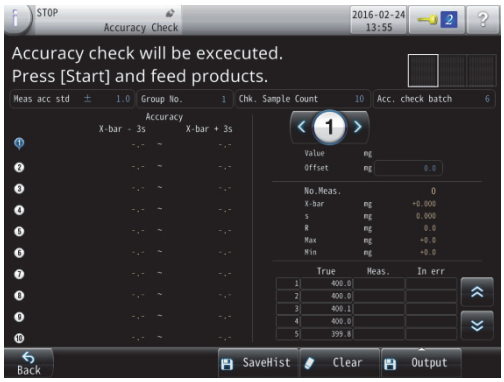

Figure 9 Accuracy Verification Screen

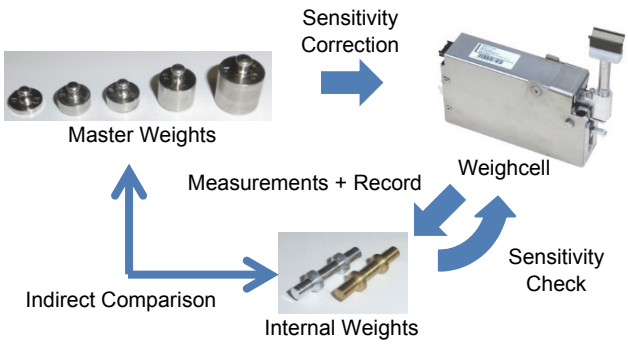

Figure 10 Diagram of Sensitivity Check Function

3.5.6 Monitoring Function

Gate operations, sensor status, signal tower status etc., are verified together. As a result, responses to operation commands to each unit and sensor can be checked, helping simplify daily maintenance and maintenance work as well as identification of failing parts.

4 Main Specifications

Figures 11 to 13 show the external dimensions of each capsule checkweigher in the series and Table 1 lists the main specifications of each model.

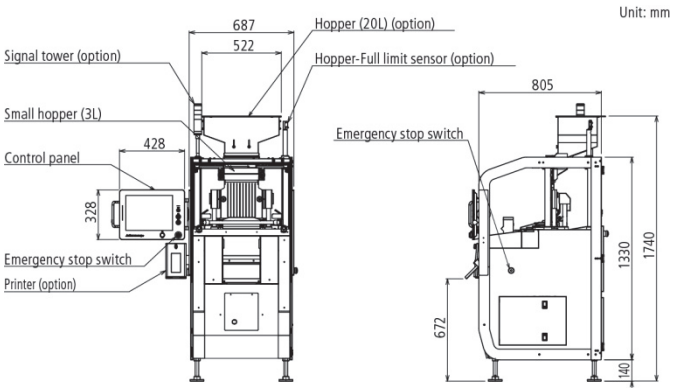

Figure 11 KWS9001AP10 External Dimensions

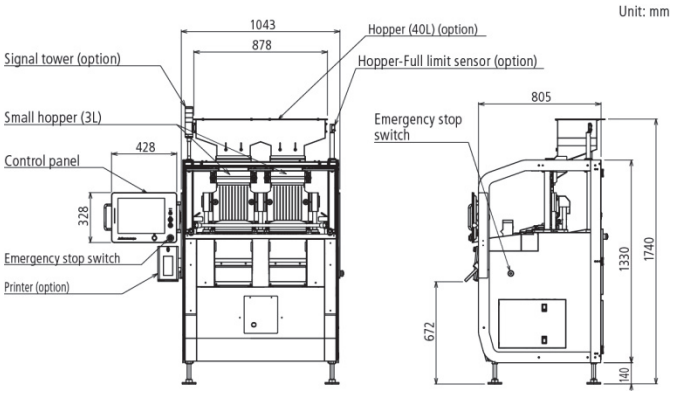

Figure 12 KWS9001AP20 External Dimensions

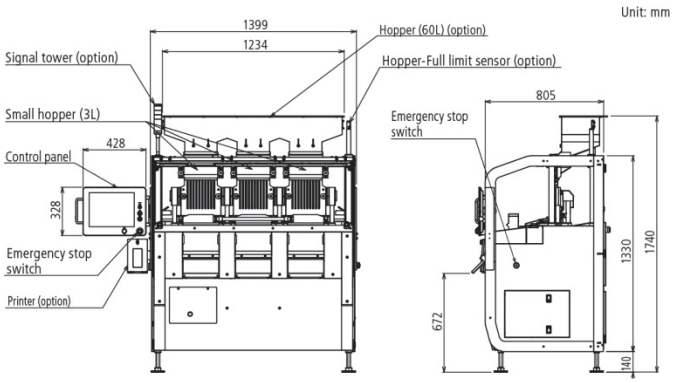

Figure 13 KWS9001AP30 External Dimensions

5 Conclusions

By supporting the electronic records and electronic signatures functions required for compliance with FDA 21CFR Part11, we have developed a new checkweigher model with rigorous quality management functions. In addition, development of a dedicated force balance weighcell mechanism supports a maximum accuracy of ±0.5 mg. As a result, we have managed to solve issues surrounding diversification of capsule raw materials with a new checkweigher supporting rejection of empty capsules and strict quality

management required for pharmaceutical products filled with high pharmacological activity drugs. Additionally, to facilitate prevention of product cross contamination caused by mixing of accumulated products and residues at cleaning, we have used an open design structure with no sharp angles as well as tool-free parts disassembly and assembly. These features help assure operators and administrators that the checkweigher is used stably and securely.

By using a force-balance weigh cell, we have reduced the impact of external vibration on selection accuracy. However, to obtain sufficient selection accuracy, it is necessary to eliminate sources of external vibration having an impact by installation on a sufficiently strong, vibration-proof floor. In addition, general-purpose gelatin capsules have a water content of 12% to 15%, while HPMC capsules manufactured using vegetable extracts have a water content of 5% to 7%, both of which change in response to atmospheric humidity levels, causing changes in capsule mass. As a result, achieving high-accuracy rejection of ±0.5 mg requires humidity management.

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Table 1 Main Specifications

Model	KWS9001AP10	KWS9001AP20	KWS9001AP30
Weight range	2 to 2000 mg		
Scale interval	0.1 mg		
Maximum throughput [1]	75,000 products/h	150,000 products/h	230,000 products/h
Lane	10 lanes	20 lanes	30 lanes
Maximum accuracy [1]	±0.5 mg		
Display	15-inch color LCD		
Operation method	Touch panel + Key (Start, Stop, and Home are direct push buttons)		
Indication range	2045.0 mg		
Preset memory	Maximum 50		
Classification [2]	4 ways (overweight/correct weight/underweight/unclassified)		
Product size	Capsule No. 000 to 5		
Power requirements [3]	100 to 115 Vac +10% −15%, single phase, 50/60 Hz, rush current 74 A (typ) (90 ms or less)		
Power consumption	550 VA	1200 VA	1800 VA
Air requirements	0.3 to 0.9 Mpa, Air supply port: nylon tube of 8 mm dia.		
Mass	350 kg	500 kg	700 kg
Environmental conditions	15 to 30°C (variation not to exceed 1°C/h to maintain accuracy), relative humidity 30 to 70% (non-condencing)		
Protection class	IP30 (IP50 for weighcell)		
Exterior	Stainless steel (SUS304)		
Data output	USB port (USB 2.0)		

1: Maximum throughput and maximum accuracy may vary depending on capsule size, filling content and quantity.

2: A rejection gate is installed per 10 lanes.

3: 120 Vac, 200 to 240 Vac are available as an option.

Note: The noise level of the checkweigher is 78 dB(A) or less.

Publicly available