

Development of World-First 100% Tablet Inspector using NIR Transmission Spectroscopy

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[Summary]

The use of inspection equipment for 100% product measurement is becoming increasingly widespread in pharmaceutical manufacturing. This trend supports the collection of production status data for active process control and helps eliminate accidental out-of-specification products. This article details the features, operating principles, basic configuration, and development points of an inspection system for 100% non-destructive inspection of tablet component quantities, cross-contamination, and foreign matter inclusion using transmission-type near-infrared absorption spectroscopy (NIR) that Anritsu is currently developing. It also introduces the technical approach to meet quality improvement requirements in pharmaceutical manufacturing.

1 Introduction

1.1 Market Background – Necessity for 100% Tablet Inspection¹⁾

Pharmaceuticals require strict quality control due to their direct impact on people's lives. They are manufactured in accordance with manufacturing management and Good Manufacturing Practice (GMP) standards established by each country.

Component analysis using High Performance Liquid Chromatography (HPLC) is utilized widely in pharmaceutical quality control. However, since it is a destructive test and requires long measurement time, some situations require sampling tests. Additionally, developing appropriate sampling plans that consider various conditions requires significant effort.

Due to these circumstances, there is a recent growing trend in introducing Process Analytical Technology (PAT), which monitors quality in real-time during the manufacturing process to improve production quality. NIR spectroscopy is an example of PAT that is widely known as a non-destructive analytical method to qualitatively and quantitatively evaluate active ingredients in tablets by utilizing light absorption spectra. It was included as a general test method in the first supplement to the 18th edition of the Japanese Pharmacopoeia promulgated in 2021. Additionally, the analytical method validation guidelines (ICH-Q2(R2)) of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) revised in 2024, added validation information for multivariate analysis including NIR. It is increasingly recognized as a standard

test method for pharmaceutical process control and Real-Time Release Testing (RTRT).

While test methods using NIR are becoming more widespread, component quantity testing remains limited to sampling applications, like HPLC. Measurement times to analyze each individual tablet range from several seconds to several tens of seconds. Considering future continuous production lines, this approach is unsuitable for inline use. Since it is difficult to capture and visualize time trend information, the possibility of occasional out-of-specification products cannot be eliminated. Out-of-specification products may occur due to unstable powder handling at the start or end of production in various manufacturing equipment, or from the mixing state of active ingredients and excipients. Additionally, the current reality is that it is difficult to control unexpected quality risks, such as pharmaceutical residue during product changeovers, mix-ups and other human errors, or the risk of foreign component contamination due to external factors. These risks could be reduced if 100% tablet inspection using NIR could be performed inline.

To solve the above-described challenges and meet the demand for quality improvement in the pharmaceutical market, we developed the world's first^{*1} NIR 100% inspection equipment using transmission (Figure 1), applying dynamic measurement and optical sensing technologies that our company has developed over more than 50 years. This article introduces our technical approach.

^{*1} based on Anritsu survey results



Figure 1 External view of NIR 100% Tablet Inspector

2 Measurement and Analysis Methods

NIR^{*2)} is a type of spectroscopic method for qualitative and quantitative evaluation of test substances by measuring and analyzing light absorption spectra in the near-infrared light region^{*2)} of the test substance.

Light absorption in the near-infrared region is weaker than absorption due to fundamental vibrations in the infrared region. Therefore, when near-infrared light is irradiated on a sample containing the test substance, light reflected from the sample surface or light transmitted through the sample can be captured. These light signals are observed in a state where some light wavelengths in specific regions have been absorbed due to the physical properties of the test substance. Non-destructive inspection of the test substance in solid samples becomes possible by analyzing and interpreting the spectrum of transmitted light containing absorption information due to the physical properties of the test substance.

^{*2)} Light generally in the 750 to 2500 nm wavelength band between visible light and infrared light

2.1 NIR Measurement Method

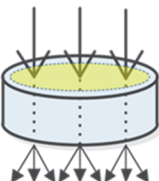
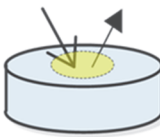
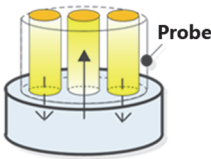
Table 1 lists NIR measurement methods. Diffuse reflection method can easily measure a large amount of light and can also yield high signal-to-noise ratio results. However, the inspection area is limited to near the surface, making it impossible to obtain information about components inside a tablet. Using interactance method, light can penetrate and inspect up to several millimeters below the surface depending on the probe configuration. However, since the probe must touch the surface of the test substance, it is difficult to apply this method to dynamic measurements, necessary for 100% inspection. This method has less measurable light compared to the diffuse reflection method, resulting in a lower signal-to-noise ratio and relatively higher technical difficulty for measurement.

The NIR 100% tablet inspector uses the transmission method to analyze components inside test tablets. This method evaluates the absorbance spectrum by comparing the intensity of the transmitted light—which carries information about the tablet’s interior—with that of the irradiated light or a reference medium, focusing on the degree of attenuation at each wavelength.

2.2 Component Analysis using NIR Transmission Spectroscopy

Analysis used measured values from NIR spectra and HPLC, etc. NIR spectra undergo preprocessing such as absorbance calculation, normalization, derivation, etc., combined with machine learning methods such as PLS and PCR, and are then compared and calibrated with HPLC measured values. This process facilitates quantitative evaluation of components in solid samples and detection of foreign contaminants in tablets.

Table 1 Comparison of NIR Measurement Methods

NIR Measurement Method	Transmission	Diffuse Reflectance	Interactance
			
Inspection Range (individual test)	Internal including surface	Only surface	Near surface
Dynamic measurement	⊙	⊙	× (Contact with test probe)

For quantitative analysis, multiple samples with known concentrations are prepared to create calibration curves. The transmission spectra obtained from each sample are analyzed and studied to create a calibration-curve model that outputs quantitative values. The concentration of the test substance is determined after feeding the absorbance spectrum into the model.

Foreign contaminants in tablets are detected using good-product control limits as a threshold. The measured absorbance spectrum containing foreign contaminants varies significantly from the thresholds established from acceptable products, which ultimately identify defective tablets.

3 Features, Basic Structure, Development Points and Implementation Method

3.1 Features

This tablet inspector evaluates the interior quality of tablets by transmitting near-infrared light through the tablet and conducting spectroscopic analysis of the light reduction. Analyzing the measured spectrum using the spectroscopic system facilitates inspection of component quantity, cross-contamination, and foreign matter contamination.

Designed for inline use on production lines, it inspects at high speeds of up to 250,000 tablets per hour. Randomly orientated tablets are fed into the machine, separated one-by-one through an alignment mechanism and then irradiated with NIR light. Transmitted light passing through tablets is measured using a spectrometer, and sorting is performed through pass/fail evaluation for each tablet using the established calibration curve.

3.1.1 Detecting Different Tablets with Similar Characteristics

The system can also differentiate tablets with similar external characteristics, which are commonly difficult to identify by traditional visual or appearance inspection. Defective products are then segregated through the machine's sorting/rejection system. This guarantees consistency in the quality of every tablet, reducing risks of leakage and cross-contamination.

3.1.2 Detecting Contaminants (Hair, etc.) in Tablets

NIR analysis is based on the principle that light is absorbed when it interacts with molecular components like CH groups in organic compounds. This method can non-

destructively detect and segregate tablets which contain foreign organic contaminants - like hair. These organic contaminants are unidentifiable using conventional devices like inspection cameras, or even metal detectors.

3.2 Basic Inspector Structure

The NIR 100% Tablet Inspector (Figure 2) consists of three main components: the transport system, the measurement system, and the operation control system.

The tablet transport system consists of supply, alignment, suction, and sorting units.

The measurement system includes a light source that emits near-infrared light, a projection unit that accurately directs this light onto the tablet, and a detector that captures the light transmitted through the tablet with efficiency.

The operation control system includes a display and functions for setting device parameters, controlling tablet transport equipment and sensors, evaluating and sorting tablets based on estimated active ingredient content, displaying statistical data, and recording operational history.

Tablet path and measurement flow are described below. Tablets are fed from the top-left hopper unit and are supplied to a succeeding vibration feeder. Broken tablets are screened through a section on the said feeder unit. Unrejected tablets are then handed to a rotary feeder and are aligned to a single file by a regulating guide. After alignment, the flat sides of the tablets stick to a negative-pressure suction disc, and their orientation is then adjusted with additional guides. Tablets sticking to the disc have their NIR spectra captured and analyzed as they pass through the measurement system. During this stage, component concentration calculations and product quality analysis are performed through signal processing. Abnormal tablets are rejected while acceptable ones are transferred from suction discs to a conveyor and discharged from the front right side of the inspector (Figure 3).

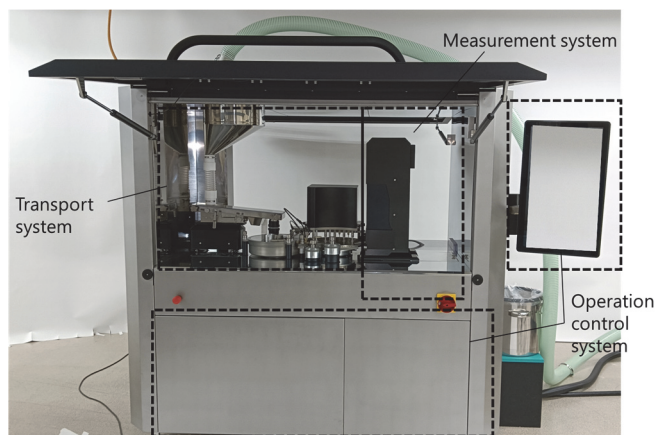


Figure 2 NIR Inspector configuration

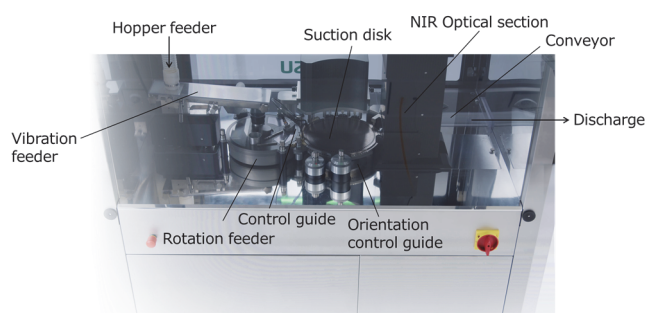


Figure 3 Tablet path

3.3 Development Points and Implementation Methods

The transmission measurement method has had challenges with poor signal-to-noise ratio due to weak measurable light. However, by developing our own optical unit, we achieved a method that can analyze tablet components non-destructively at a higher speed. (Figure 4).

Assuming inline use on production lines, the high-speed inspection system targets a maximum capacity of 250,000 tablets per hour. We achieved a processing time of ≤ 11 ms per tablet by using high-speed measurement, evaluation, handling, and sorting technologies.

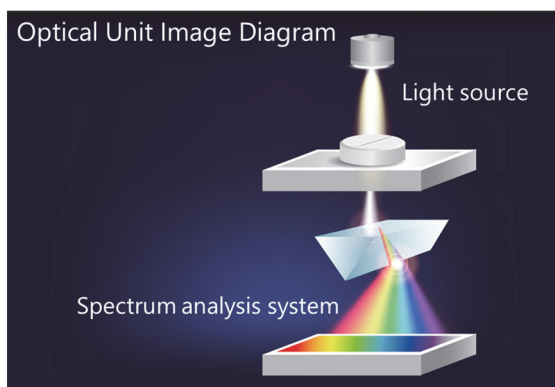


Figure 4 Optical unit

3.3.1 High-Speed Measurement and Evaluation Processing

Achieving a processing capacity of 250,000 tablets per hour requires processing each tablet within 11 ms. Furthermore, since tablet orientation must be detected in < 1 ms, precise timing detection required development of an FPGA-based dedicated detection mechanism. Timing-based measurement captures the near-infrared spectra, and signal processing is performed according to pre-registered methods to perform pass/fail evaluation and sorting. Each measurement, evaluation, and sorting process are designed to use a separate processing mechanism so as not to cause interfere to each other.

3.3.2 Handling

Stable and accurate measurement of transported tablets requires controlling tablet orientation, position, vibration errors, and speed fluctuations. This handling system uses guides to minimize variations that occur to tablets when they stick to the suction disc. This enables measurement accuracy, achieving circumferential deviation within ± 0.2 mm, orientation angle variation within 3° , and speed fluctuation rate through the suction disc mechanism within $\pm 0.5\%$.

3.3.3 Sorting/Rejection

The inspector requires sorting/rejection equipment to ensure that both uninspected and defective tablets are reliably rejected from the line, while simultaneously preventing anything else other than acceptable tablets from transporting to the next stage. Figure 5 shows the sorting/rejector arrangement.

Air-jet rejectors are used to sort out defective tablets from about 90 tablets transported per second based on the pass/fail evaluation results, achieving tablet sorting within 11 ms by using fast-response solenoids and optimizing the flow path.

Additionally, the sorting unit has air-jet rejectors on the downstream side of the defective-tablet rejection, which ejects uninspected tablets. Furthermore, a physical flipper-style gate downstream of the complete discharge section sorts improperly sorted defective tablets, ensuring that defective or uninspected tablets never flow to the acceptable tablet side.

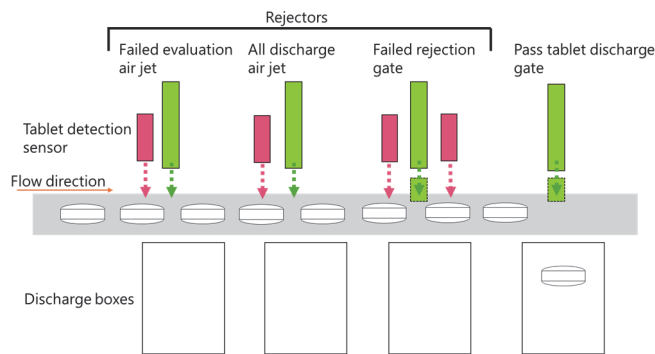


Figure 5 Sorting/Rejector configuration

3.3.4 Efficient Productivity

In addition to the 100% inspection function, there are the following: a function to register settings according to tablet types as product varieties; a NAVI function to support product registration in a guided format; an adjustment function to limit variation in results due to operator skill levels, enabling high-reproducibility measurements; and calibration curve creation software for converting NIR spectra to component concentrations.

3.3.4.1 Product Inspection Records NAVI

Tablet registration is completed by following the work process guided by the navigation-style screen (Figure 6). Time requirements are reduced, and work efficiency is improved by automatically calculating the optimal values for various parameters.

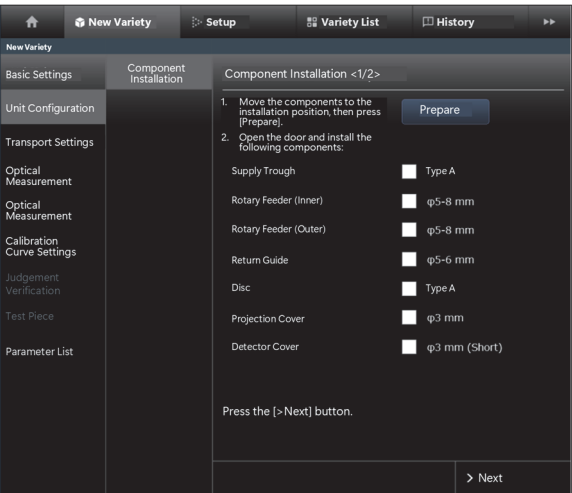


Figure 6 Navigation-style operation screen

3.3.4.2 Tablet Orientation Adjustment Control Function

To improve measurement reproducibility, tablets must be transported in a stable orientation. However, since tablet shape and thickness vary, the orientation of each tablet must be adjusted individually. This inspector uses guides to adjust tablet orientation, and a camera confirms the position

adjustment accuracy. This high-speed camera positioned beside the suction disc visually monitors the orientation of tablets during transport. The orientation can be easily and intuitively adjusted by aligning the tablets within the marker lines shown at the top and bottom of the camera image, using guide adjustments (Figure 7).

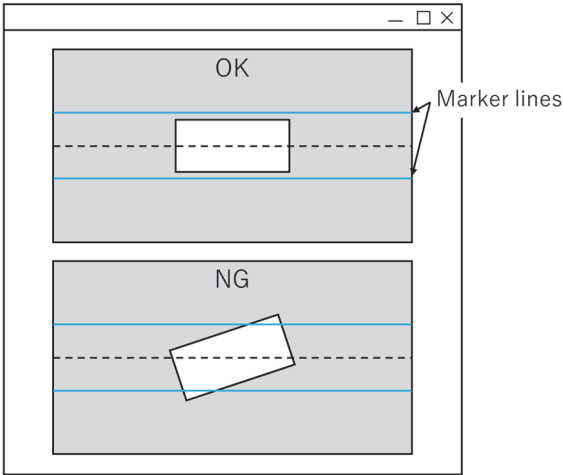


Figure 7 Tablet orientation control adjustment function screen

3.3.4.3 FDA 21CFR PART11 Support

The FDA 21CFR Part 11 regulation established by the Food and Drug Administration (FDA) concerns ‘electronic records and electronic signatures,’ and requires audit trail records and user authority management, among other things, as requirements for electronic records to secure reliability equivalent to paper records. This inspector has an audit trail and qualified person authentication functions in compliance with FDA 21CFR Part 11.

The audit trail function records the history of operations and errors related to production and documentation within the equipment, which can be used to monitor deviations from manufacturing procedures and analyze causes of abnormalities. Additionally, statistical data can be saved as production records linked to production lot numbers.

The qualified person authentication (user authentication) function requires a user code and password for operation. Unauthorized operations are prevented by setting permissions for each user. Additionally, operation permissions can be customized according to customers’ management standards.

3.3.4.4 Calibration Curve Software

Calculation of component amounts from NIR measured results requires preparing multiple tablets and creating a

calibration curve (Figure 8) establishing the correlation for estimating actual component amounts from NIR spectra.

Obtaining an appropriate calibration curve for each target tablet requires expertise in preprocessing (Figure 9) multiple parameters, such as filtering, normalization, and differentiation processing. This inspection machine has analysis software to create calibration curves (processing to calculate component amounts) from NIR spectra - reducing the work burden on users by parameter adjustment assistance features.

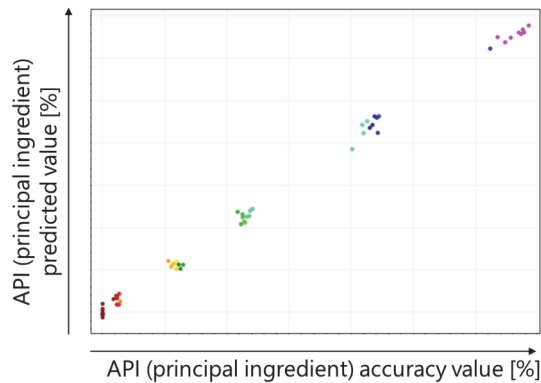


Figure 8 Calibration curve

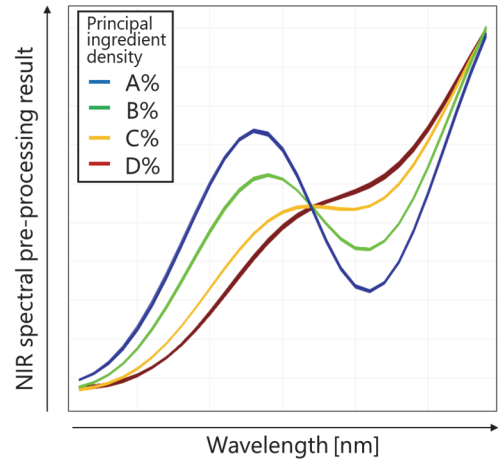


Figure 9 NIR Spectral preprocessing results

3.3.5 Sanitation

The main base is mirror-finished so potential blind spots are visible from reflections. Parts that mate with the main base are tapered, creating a shape (Figure 10) that prevents powder residue accumulation and is easy to clean.

Components, such as frames, are designed with sanitation in mind by making them solid rather than hollow. Parts that touch tablets and require daily cleaning can, with few exceptions, be detached and reattached without tools, allowing easy cleaning.

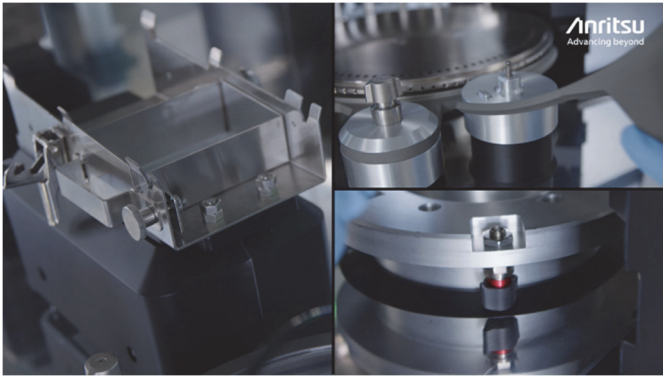


Figure 10 Main base and parts with powder buildup resistant design

4 Key Specifications

Table 2 Key Specifications

Item	
Supported tablets	Type: Uncoated Shape: Flat disk, R type Diameter: ≤5 to 12 ±0.2 mm Thickness: ≤2 to 5 ±0.2 mm Hardness: ≥39 N
Maximum inspection speed	250,000 tablets per hour (Depends on tablets)
Main unit dimensions	1600 W × 1000 D × 1800 H mm
Mass	1200 kg
Display section	23.8-inch IPS LCD (Full HD)
Operation section	Touch panel (Capacitive)
External frame	SUS304, A5052, PET
Settings	1000 product types
Operating environment temperature	20° to 26°C (<1°C per hour temperature change)
Operating environment relative humidity	40% to 60% (No condensation)
Power source and consumption	3-phase 200 Vac ±10% 50/60 Hz 80 A
Waterproof standard (IEC 60529)	IP30 (Including operating section)

5 Conclusion

Inspection of all tablet interiors is now realizable through this inspector which uses high-speed NIR transmission technology. Until now, 100% inspection of tablets before packaging has primarily been surface-appearance inspection, but going forward, it will be possible to inspect the ‘interior’ of all tablets (constituting most medication tablets), thus enabling supply of higher-quality pharmaceuticals. On the other hand, recent labor shortages do not help prevent careless

mistakes using meticulous quality assurance by human hands.

Going forward, we aim to expand the range of tablets supported by this inspector, as well as improve usability for practical implementation by using automation to solve labor shortage issues while still ensuring pharmaceutical quality.

Appendix

The results of the calibration curve obtained using this equipment are recorded here for reference. We created a calibration curve model using one-half of 116 tablets from six types of acetaminophen formulation as training data under the calibration curve creation conditions listed in Table 3 and then tested the created model with the remaining tablets. The error in quantitative value prediction (RMSEP) was within $\pm 1.5\%$ (Figure 11).

The ‘Sakura Bloom Tablets P2 Mock’ model for creating Common Technical Documents (CTD) for pharmaceutical applications using RTRT uses $RMSEP \leq 1.5\%$ as the accuracy criterion for validating calibration models created using NIR. We confirmed that actual measurement data using real drugs with this inspector satisfies the above criteria.

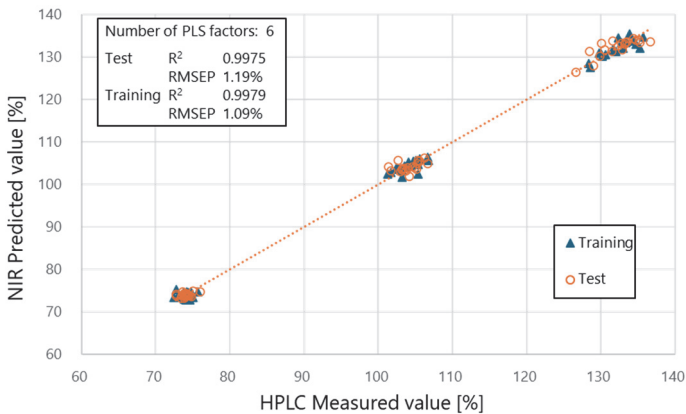


Figure 11 Plot of quantitative values obtained by NIR and HPLC measurements

Table 3 Calibration Curve Conditions

	Training Data	Test Data
R ²	0.9979	0.9975
RMSEP	1.09%	1.19%
Sample size	58	58
Preprocessing	SNV+2 Sub differential	
Wavelength range	1005 to 1178 nm	
Frequency domain	8488 to 9950 cm ⁻¹	
Repeatability (3σ)	1.40%	

References

1) Japan Society of Pharmaceutical Machinery and Engineering, 134th issue, “Transmission Near Infrared Spectroscopy-Based Inspection Machine, Capable to Inspect Interior of Tablets at a Rate of 250,000 Tablets per Hour”

2) The Japanese Pharmacopoeia, 18th Edition, The Ministry of Health, Labour and Welfare, Japan, 2021.

3) Sakura Bloom Tablets P2 Mock

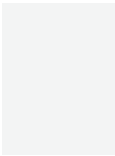
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