# Development of X-ray Inspection System for Pharmaceutical Products

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[Summary] Due to changes in pharmaceutical packaging and administration methods, external monitoring equipment such as CCD cameras and earlier generation X-ray inspection systems have issues with inspecting new packaging methods. To solve these new problems, we have developed the KD7490LYN X-ray inspection system for pharmaceutical products. This system uses low-energy X-rays of a specific wavelength to achieve high-accuracy and high-stability inspection of pharmaceuticals based on Anritsu's long experience in X-ray inspection of food products and our unique signal-processing technology.

## 1 Introduction

X-ray inspection has become increasingly well known and popular in the food processing industry since 2000 as an effective procedure in manufacturing processes. More recently, it is starting to be introduced as an inspection method in the pharmaceutical business world. As pharmaceuticals become more globalized, there is increasing use of aluminum foil packaging due to its excellent barrier functions, but this has caused problems with confirming the contents of foil packages by previous external inspection methods using CCD cameras, etc. Additionally, due to revisions of Japan's domestic pharmaceutical laws, there is an increasing need to inspect the internal contents of foil packages that can now be manufactured by outside consignment contract methods. On the other hand, with progress in the development of new medication methods, medical products are becoming far more diverse. Table 1 shows the trend in pharmaceutical product forms and resulting package inspection issues. New product forms range from transdermal absorption of drugs through the skin to fast disintegrating tablets taken orally and there are issues with inspection of these products using X-ray inspection systems developed principally for the food-processing industry.

Anritsu offers various types of quality inspection solutions using food X-ray inspection systems and has applied this experience to issues with foil-packaged pharmaceuticals, such as poorly packaged transdermal patches and missing tablets in packaged fast-disintegrating oral tablet packages. This article introduces the company's KD7490LYN X-ray Inspection System newly developed for pharmaceutical products.

Table 1 Trend in Pharmaceutical Product Form and Package Inspection Issues

| Trends in pharmaceutical packages | Packet inspection issues |
|---|---|
| Increasing use of aluminum foil packages with high barrier functions suppressing aging during storage | Inability to confirm contents using CCD camera because packaging not transparent |
| Increasing use of transdermal medications (patches applied to skin for drug delivery) | Need to detect patch trapped in sealed part of package but patched thinness makes accurate detection difficult using conventional X-ray inspection systems because difference between patch and package density unclear |
| Spread of fast orally disintegrating tablets | Need to detect presence of tablets in package but low- density materials make accurate detection difficult because unable to detect differences in density between tablets and package |

Figure 1 External view of KD7490LYN

## 2 X-Ray Inspection System

X-ray inspections systems irradiate the inspected product with X-rays and use the resulting captured X-ray transmission image to detect the presence of contaminants; they are used on production lines for food products, etc., to automate the inspection process for every product on the line. Due to their ability to detect broken items or missing within packaged products that cannot be seen by visual inspection, they are used by many different types of production line.

Instead of using statistical sampling inspection on lines producing large numbers of products with individually packaged items purchased by consumers, it is now becoming more common to install inspection equipment on the line to inspect the quality of every product on the line. Not only does this reduce the number of faulty products reaching the market but it also provides data on the timing and trends in production of faulty products, helping spot production line problems early and increasing line efficiency.

### 2.1 Operation Principle

An X-ray inspection system is composed of an X-ray source, a line-sensor type X-ray detector, and a conveyance mechanism, such as a belt conveyor. Figure 2 shows the structure of a general, in-line type, X-ray inspection system. A beam of X-rays output from the X-ray tube is radiated at the belt conveyor and detected by the X-ray detector under the belt conveyor. As inspected products pass along the belt above the detector, they block some of the X-rays passing through them to form a transmission image captured at the detector. The presence of contaminants in the food products, etc., is detected by subjecting the captured transmission image to image-processing algorithms, assuring high-accuracy contaminant detection with no effect on the food[1].

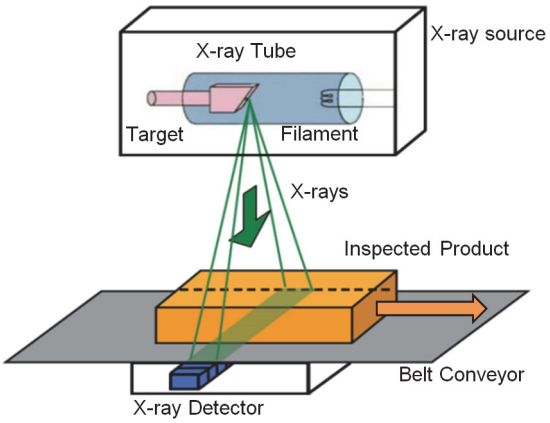


Figure 2 Principle of X-ray Inspection System

Figure 3 shows a schematic of the X-ray transmission penetration when inspected products are irradiated with X-rays. As seen in the figure, the X-rays from the X-ray source are attenuated by passage through the material of the inspected product and any foreign materials in it. The degree of attenuation depends on the atomic number and density of the constituents as well as the thickness. When the mathematical product is large, or when the thickness is thick, the degree of X-ray attenuation is high. As shown in Table 2, common food contaminants, such as metals, stones, etc., have a high value for this mathematical product compared to the food material, so the amount of X-rays passing through the food where contaminant is present is much less than the amount passing through the food itself.

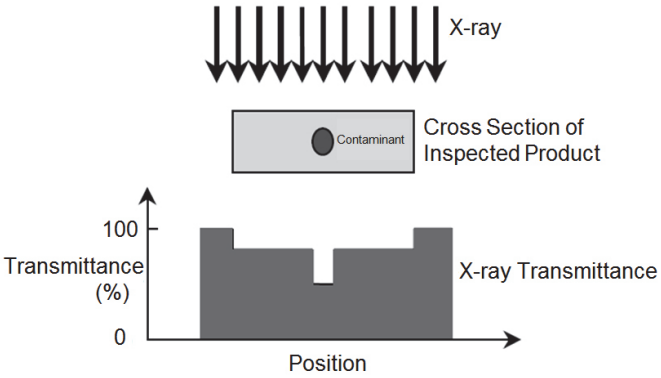


Figure 3 X-ray Penetration Amount

Table 2 Elements and Transmittance

| Material | Common elements in food | | Common elements in contaminants | |
|---|---|---|---|---|
| Element | Hydrogen | Carbon | Silicon | Iron |
| Atomic number | 1 | 6 | 14 | 26 |
| Density [g/cm$^3$] | 0.1 | 2.3 | 2.3 | 7.9 |
| Atomic number × density | 0.1 | 14 | 33 | 204 |
| Degree of attenuation (transmittance) | Low (High) ⟷ | | | High (Low) |

The theoretical explanation for this phenomenon is explained below. When a product is irradiated with X-rays with energy $I_0$, the energy of the X-rays after passage through the product, $I$, is found from the following equation, where $\mu$ is the material total absorption coefficient, and $d$ is the thickness of the material.

$I/I_0 = e^{\mu d}$ (Decay Law)

Additionally, the total absorption coefficient $\mu$ is found from the following equation, where $\lambda$ is the X-ray wavelength, $\rho$ is the material density, $Z$ is the material atomic number, and $C$ is a constant. From this, we can see that the X-ray transmittance changes with the inspected product and contaminant atomic number, thickness, and density.

$$\mu=\lambda^3\rho CZ \quad (\mathrm{cm}^{-1})$$

Furthermore, shorter-wavelength X-rays (at higher X-ray tube impressed voltage) have a lower absorption coefficient, so the X-ray transmittance increases[2),3),4)].

## 3 Development Points and Implementation

In addition to resolving the issues with packaged products listed in Table 1, the main point of this development was to build a system that could be easily introduced into a production line for pharmaceutical products to ensure strict quality control.

### 3.1 Pharmaceutical Product Package Inspection Issues

Transdermal medications with a diverse variety of forms are becoming widespread. They are generally composed of a thin patch type base film coated with medication covered by another film called a liner to protect the medication and an adhesive covering the medication surface all packaged in a sealed rectangular form using an aluminum-laminate film, etc. Sometimes, at the sealing stage, the patch can be trapped between the sealing materials, causing it to be incompletely packaged and requiring it to be discarded because the incomplete packaging is unable to maintain the quality of the medication. Additionally, orally fast-disintegrating tablet medications are becoming more commonplace. These tablets are designed to dissolve in very small amounts of water, so they are commonly packaged in aluminum foil with high resistance to humidity. Consequently, it is important to inspect these packages for missing tablets and failed packaging with high accuracy and stability at the inspection stage after packaging.

Current medications, including these two examples, generally use packaging composed of polypropylene (PP), polyvinyl chloride (PVC), aluminum, etc., with thicknesses of 30 to 400 µm, requiring X-ray inspection technology able to capture the transmission images of packaging materials and tablets/patches with different densities.

### 3.2 Implementation Procedure

#### 3.2.1 X-ray Management for Pharmaceutical Packages

Figure 4 shows a sample of packaged tablets. To give a better understanding of the actual package, it is shown as a cross-section diagram.

Figure 5 shows the difference in the X-ray transmittance of aluminum and polyvinyl chloride. As is clear from the figure, at X-ray energies above 40 keV, the X-rays pass completely through the product, making evaluation difficult. Consequently, it is important to use X-rays with an energy level of less than 40 keV to be able to discriminate between the 20-µm thick aluminum and 60-µm polyvinylchloride used in the packaging and the medication.

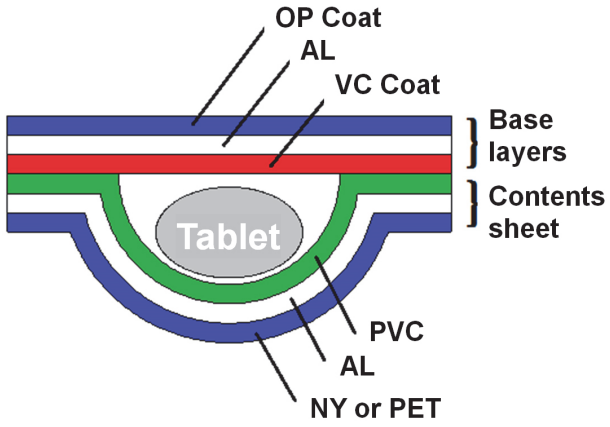


Figure 4 Pharmaceutical Product Packaging

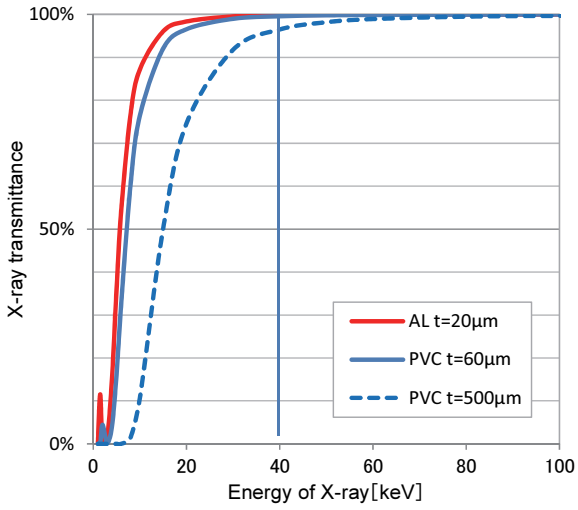


Figure 5 X-ray Transmittance

As a result, this newly developed X-ray inspection system uses low-energy X-rays of less than 40 keV to achieve high-accuracy and stable measurement with better ability to differentiate between the densities of the packaging mate-

rials and contents of pharmaceutical products. Figure 6 compares the transmittance image of a package transdermal patch obtained with this newly developed inspection system and a previously developed system. The transmission image on the left was obtained with this system, while that on the right was obtained with an earlier X-ray inspection system. As is clear from the figure, the newly developed X-ray inspection system can discriminate between the patch and the package.

Based on this result, the KD7490LYN can inspect transdermal patch packages with extremely high effectiveness. Although this paper does not show actual examples of images, we were also able to confirm the effectiveness of the system for inspecting orally fast-disintegrating tablet packages as well.

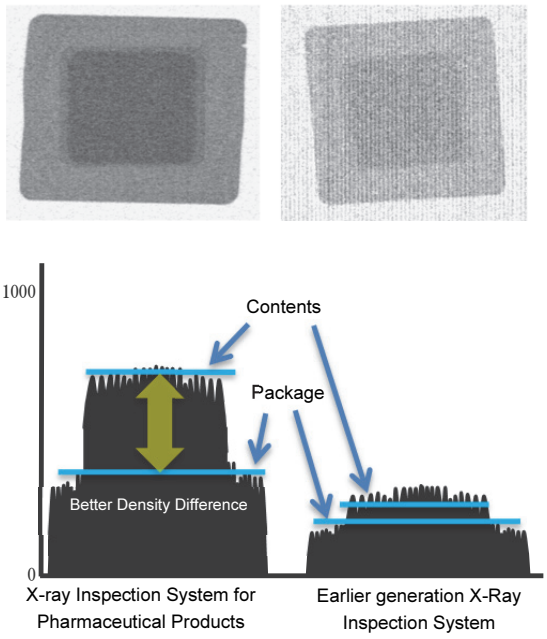


Figure 6 X-ray Penetration Picture and Density

### 3.2.2 Inspection Conveyor

The belt conveyor carrying inspected products is divided into two parts on this inspection system; the top surface of the conveyor exposed to X-ray irradiation is configured without a conveyor belt, eliminating conveyor-belt noise, which helps to differentiate fine density differences in the transmittance image between the very thin transdermal patch material and the packaging, enabling evaluation with better margins.

Additionally, although previous X-ray inspection systems usually have a protective curtain to block X-ray leaks, since this system only uses low-energy X-rays with a maximum output of 15 W (compared to lowest 60 W output of current Anritsu models), there is no need for a protection curtain. Eliminating the protection curtain due to the low X-ray output solves the problems of very lightweight inspected products, such as medications, either being damaged by hitting the curtain or becoming jammed inside the inspection system due to the weight of the curtain. This helps prevent evaluation mistakes and mis-rejections due to problems with downstream rejector timing, thereby assuring more precise inspection (Figure 7).

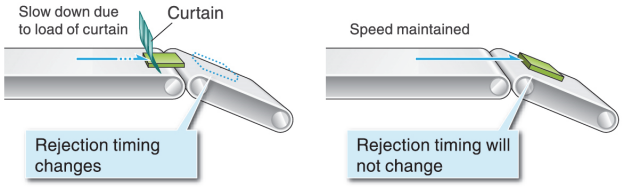


Figure 7 Effect of Protection Curtain

### 3.2.3 Design for Pharmaceutical Production Lines

To facilitate introduction of the new system into existing production lines, we designed the new unit with a compact overall length of just 550 mm. This is 60% shorter than the length of previous Anritsu X-ray inspection systems with an X-ray protection curtain (Figure 8).

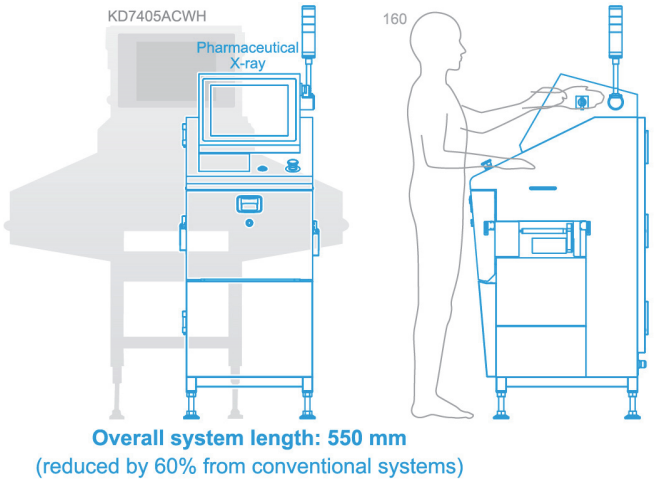


Figure 8 Shorter Length Design

### 3.2.4 Validation Support

Since pharmaceutical products are intimately related to human life, their safety and effectiveness must be assured by the best quality control. As a result, it is necessary to ensure that each batch is always manufactured to the same quality standards, which is generally called product validation[6]. Validation in Japan is regulated on the basis of Article 13 of the GMP ordinance related to manufacturing and

quality control of pharmaceutical and quasi-pharmaceutical products under the legal requirements for pharmaceutical plants. This X-ray inspection system is subject to these requirements and must be inspected for compliance when introduced to a pharmaceutical production line. The contents differ with each user and cover a wide variety of areas such as confirming the operation and function of the instrument by consultation with the user and using various documents related to quality control systems and operation. To meet these demands it is important to have extensive knowledge and experience about validation procedures, which Anritsu has accumulated through many years of developing and delivering checkweighers and auto-checkers for pharmaceutical capsules, etc., to the pharmaceutical industry. Based on this experience we have incorporated all the necessary validation functions into this new X-ray system while also establishing a support system for operational testing and installation, etc.

### 3.2.5 Safety Design

To assure the safety of operators using this system on production lines we have implemented the following safety design features.

(1) Safety Level 1 X-ray Leakage Exposure

Since exposure to X-rays beyond defined levels has a serious impact on human health, devices generating X-rays are regulated by law according to the amount of X-ray leakage. In Japan, the ordinance on prevention of ionizing radiation (Ministerial Order 51, September 30, 1982) requires establishment of a controlled zone where the 3-month exposure dose shall not exceed 1.3 mSv. However, this newly developed system has been designed and manufactured to ensure that the X-ray leakage level does not exceed the set standards and does not require establishment of a control zone.

(2) Safety Level 2 Built-in Safety Devices

To ensure the safety of operators in unexpected circumstances, such as when a problem occurs on a production line, this inspection system has been designed with the following six safety device interlocks to prevent accidental exposure to X-rays (Figure 9).

[1] X-ray generation ON/OFF key

X-ray generation is stopped completely when this key is set to OFF.

[2] X-ray cover Open/Close interlock

An interlock mechanism stops X-ray generation completely when the covers of the system are open.

[3] X-ray blocking covers

The covers are constructed so that they can only be opened when X-ray generation is stopped completely using the ON/OFF key described above.

[4] Emergency stop switch

Pressing this switch cuts power to the belt conveyor and the X-ray generation source, completely stopping the operation of both.

[5] X-ray radiation notification display

A lit tower lamp notifies everyone in the area when X-rays are being generated.

[6] Hand-insertion sensor

X-ray generation is stopped if this sensor is interrupted for some fixed time buy insertion of a hand, etc.

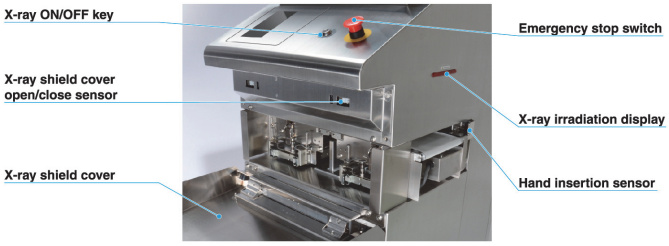


Figure 9 Safety Devices

### 3.2.6 Safety of Inspected Products

X-rays are high-energy waveforms and part of the electromagnetic spectrum. They do have the potential to affect inspected products. As a consequence, the Ministry of Health and Welfare established guidelines (Ministry of Health and Welfare Notice 370, December 28, 1962) governing exposure of foodstuffs and related materials, setting the permissible limit to 0.10 Gy for food manufacturing and processing plants. On the other hand, pharmaceutical manufacturers wanting strict quality controls have hesitated to introduce X-ray inspection systems because there is no documentation about basic standards for pharmaceutical products.

As a result, we worked with a laboratory at Nagoya University to examine the effect of X-ray radiation on pharmaceutical products. We picked three types of commercially available nonsteroidal anti-inflammatory drugs (NSAID): acetoaminofen 300 mg, loxoprofen 60 mg, mefenamic acid 250 mg and X-rayed each sample under the following 4 conditions.

- 0.34 mGy equivalent to three times normal inspections (the reference value)
- 0.10 Gy, the safety limit of Food Sanitation Act (about 300 times the reference value)
- 0.50 Gy, the level of having an effect on human blood cells (about 1,500 times the reference value)
- 300 Gy, a huge dose of radiation (about 9,000,000 times the reference value)

The samples were also subjected to pharmaceutical tests in accordance with the guidelines of the Japanese pharmacopoeia (drug contents, solubility, disintegration, hardness, mass, external appearance, sensory feel) along with accelerated aging tests (40°C, 75% RH, 1, 3, 6 months).

The results confirmed that the drug contents and properties were unchanged after irradiation under all conditions (Figure 10). The changes compared to the non-irradiated controls were within the permissible ranges, confirming that irradiation had no effect[7].

Although it may be necessary to confirm safety for specific pharmaceuticals when introducing this system, based on the above results, we can say that the extremely low dose rates used by this equipment do not have any effect on pharmaceutical products.

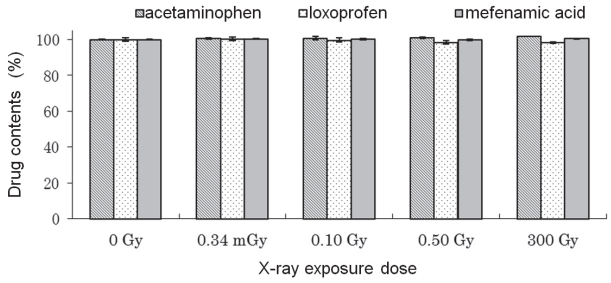


Figure 10 Drug Content Test Results

## 4 Main Specifications

Figure 11 shows the external dimensions of the KD7490LYN X-ray inspection system for pharmaceutical products and Table 3 lists the main specifications.

Table 3 Specifications

| | |
|---|---|
| Model | KD7490LYN |
| Inspection items | Missing tablets in PTP package, extra tablets in package, trapped products in package materials |
| X-ray output | 15 W max. |
| Safety | X-ray leakage of less than 1 μSv/h,<br>X-ray leakage prevention safety devices |
| Display method | 15-inch color TFT |
| Operation method | Touch panel |
| Inspected product size | 100 (W) × 30 (H) × 230 (L) mm max. |
| Number of products | 100 max. |
| Belt conveyor speed, maximum conveyed weight | 10 to 40 m/min, 0.5 kg max. |
| Power supply | 100 to 120, or 200 to 240 Vac, single phase, 50/60 Hz |
| Power consumption | 300 VA |
| Mass | 160 kg |
| Usage environment | 10° to 30°C, 30 to 85% RH,<br>700 to 1060 hPa air pressure, no condensation |
| Waterproof level | IP30 |
| External finish | SUS304 |

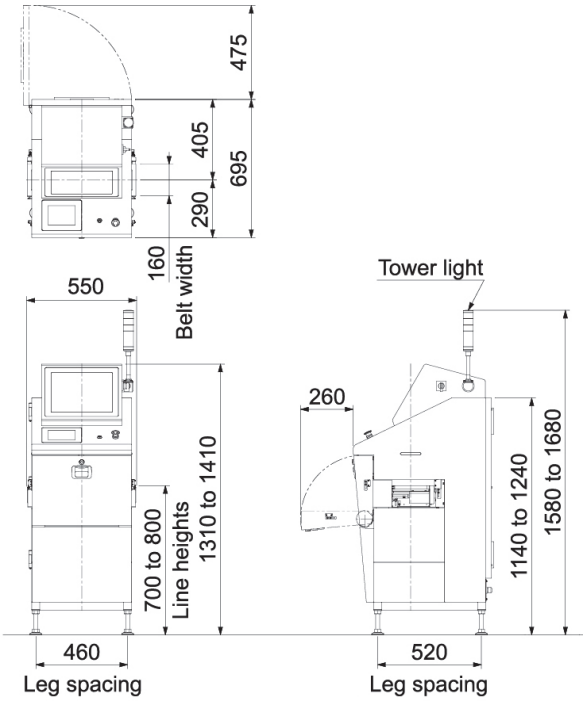


Figure 11 KD7490LYN Dimensions

## 5 Summary

We have developed a high-accuracy and stable X-ray inspection system for inspecting pharmaceutical products using X-ray control and belt conveyor technologies solving the problems of inspecting packaged pharmaceuticals that are difficult to inspect using external visual techniques such as CCD cameras and earlier-generation X-ray inspection systems. Additionally, we clarified the effect of X-ray radiation on pharmaceutical products to demonstrate the possibilities of inspecting the diverse range of new pharmaceutical packages to pharmaceutical manufacturers requiring strict quality control systems.

Anritsu aims to become a leading partner in product quality control assuring the safety and reliability of foods and pharmaceuticals by offering new quality-control solutions meeting its customers' needs.

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