Production Management of Sterile Medical PDT Probes

Koichi Akiyama, Takeshi Akimoto

[Summary] One in two Japanese living today can expect to suffer from a malignant tumor (cancer), which has been the leading cause of death since 1981 and is responsible for 30% of all deaths. The three main treatments for cancer are surgery, chemotherapy, and radiotherapy with surgery occupying 70% of treatment. However, Treatment involves pain and preserve internal organs is difficult, while the other chemotherapy and radiotherapy methods suffer disadvantageous side-effects, causing a huge burden for patients. Therefore, photodynamic therapy (PDT: Photodynamic Therapy) in which a photosensitizer agent is administered as a treatment for reducing the burden on a patient and laser light irradiation is performed on the lesion has attracted attention. This article outlines PDT medical-grade semiconductor equipment developed by Anritsu in cooperation with Meiji Seika Pharma Co., Ltd. It describes production methods and production environment management for the single-use EC-PDT probe to be used in conjunction PDT semiconductor laser developed for treating esophageal cancer. To assure production of a sterile EC-PDT probe with sufficient consideration from both hygiene and quality aspects, we configured unique manufacturing and quality management systems.

1 Introduction

Malignant tumors (cancers) occur as a result of the uncontrolled autonomous proliferation of cancerous cells, which either invade adjacent tissues or spread through the body by metastasis. Malignant tumors have been a main cause of death in Japan since the early 1900s and became the leading cause from 1981.

The treatment for malignant tumors is early discovery followed by surgical removal, chemotherapy, and radiotherapy.

In addition to these treatments, there are also supplemental treatments, such as immunotherapy, Photodynamic Therapy (PDT), etc.

Among these treatments, PDT has recently become a drawn attention of cancer treatment and Anritsu manufactures medical equipment for PDT.

This article explains PDT and outlines our medical equipment. It also describes management of medical equipment production methods and the production environment to achieve safe stable products.

2 About PDT

PDT is a cancer treatment performed using a combination of a photosensitizer agent with an affinity for malignant tumors and laser light.

As shown in Figure 1, photosensitizer agent accumulates selectively in tumorous tissues after waiting for a fixed time interval following perfusion. Subsequent irradiation with laser light causes a photochemical reaction and the resultant free oxygen radicals denature and destroy the tumor.

Since the lifespan of free oxygen radicals is very short, they have a very small dispersion range and selectively attack only the tumor but not other healthy tissues.

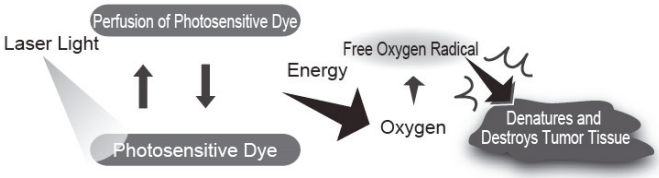

Figure 1 PDT Principle

Three photosensitizer agent—porfimer sodium, talaporfin sodium, and verteporfin—have been approved as PDT medical agents in Japan. Talaporfin sodium (LASERPHYRIN®, Meiji Seika Pharma Co. Ltd.) is approved for treatment of early stage (stages 0 to 1) lung cancer, primary tumor brain cancer (only on condition of performing lumpectomy), and for localized recurrence of esophageal cancer following chemotherapy or radiotherapy.

The photosensitizer agent is easily broken down by a photoreaction induced by laser light at a wavelength with high optical absorption properties. Consequently, a laser

device for PDT must be able to radiate laser light of a specific wavelength.

3 PDT Laser Equipment

Laser devices for PDT using PDT excimer lasers, PDT semiconductor lasers, or PDT lasers for ophthalmology are defined as medical equipment.

Figure 2 shows an example of our company's medical equipment (Meiji Seika Pharma's HPL010B PDT semiconductor laser) using in combination with talaporfin sodium, which has high optical absorption properties for a laser wavelength of 664 nm, but which is hardly absorbed by hemoglobin.

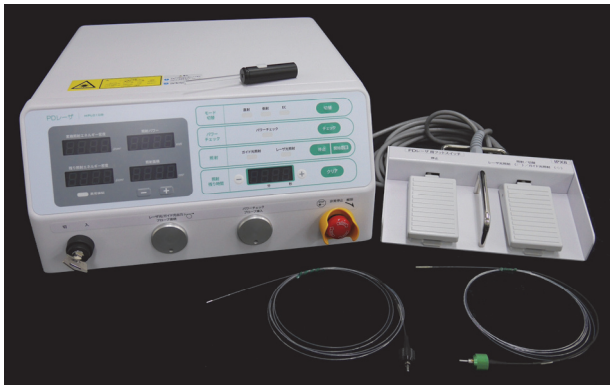

Figure 2 HPL010B PD Laser Equipment

Consequently, the HPL010B PD laser uses a semiconductor laser with an output wavelength of 664 nm and uses both temperature and level control to achieve a high-stability output wavelength and power.

A PDT probe composed from optical fiber is used to irradiate the tumor with accumulated photosensitizer agent directly with laser light. During PDT treatment, usually the PDT probe is guided from the Forceps port of an endoscope opening to irradiate the tumor tissues with laser light.

The output level at the tip of the PDT probe can be set in the range between 75 and 500 mW and a stable output is obtained using a self-check immediately before use. At PDT treatment, the irradiation time is set automatically and laser output stops automatically when the set time has elapsed, preventing excess irradiation with laser light. In addition, the laser light can be switched ON/OFF using a foot switch coupled to the main screen even when busy with other procedures during PDT treatment.

An example of PDT treatment is shown in Figure 3.

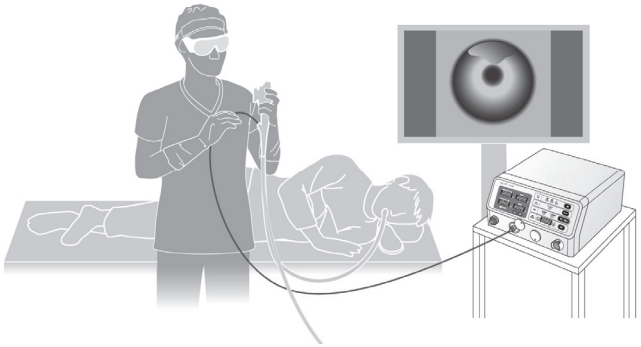

Figure 3 Example of PDT Treatment

There are three types of PDT probe depending on the tip irradiation direction and beam width: a direct-irradiation probe; a side-irradiation probe; and an EC-PDT probe, providing the best choice based on the target disease, lesion size, and position.

For treating early stage lung cancer, the PDT probe (direct- or side-irradiation probe) is connected directly to the PD laser.

The direct-irradiation probe radiates laser light directly forward from the probe tip. The side-irradiation probe radiates laser light in a radial direction relative to the probe optical propagation direction. The best probe to irradiate the lesion with surety is chosen for treatment.

Figure 4 shows the irradiation range for the direct- and side-irradiation probes.

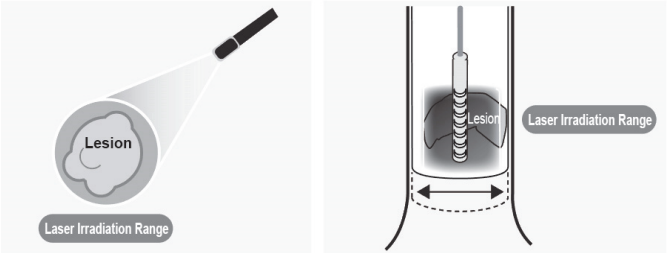

Figure 4 Laser Irradiation Range; Direct-Irradiation Probe (L); Side-Irradiation Probe (R)

Figure 5 shows the EC-PDT Probe used for treating localized recurrent esophageal cancer and Figure 6 shows the EC-PDT probe laser irradiation range.

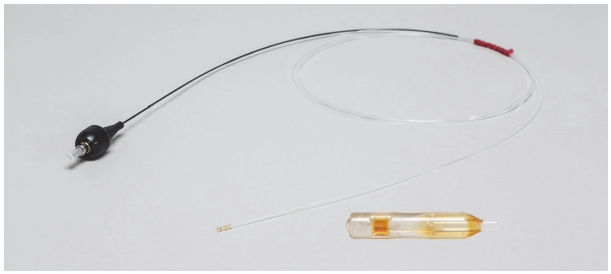

Figure 5 HPP003A EC-PDT Probe

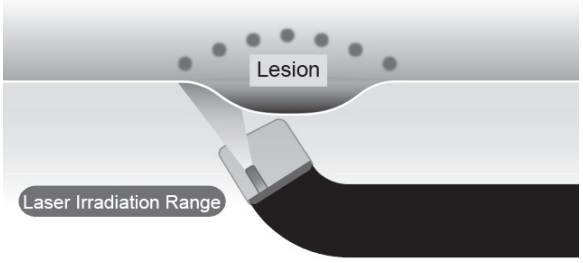

Figure 6 EC-PDT Probe Laser Irradiation Range

This EC-PDT probe is defined as a single-use probe for PDT semiconductor lasers and has been approved by the Ministry of Heath, Labour and Welfare as a similar medical device to a PD laser.

The EC-PDT probe radiates laser light directly forward from the probe tip in the same manner as a direct-irradiation probe. The main difference from the direct- and side-irradiation probes is the probe sterilization process to assure cleanliness.

At probe sterilization, it is important that bacteria cannot adhere to the probe and multiply. Consequently, hygiene is considered and re-examined at every stage when manufacturing the EC-PDT probe. The sterilization method, assembly parts, storage, management and work environments, personnel environment, workshop facilities and tools, production procedures, etc., must all be examined.

4 Manufacturing EC-PDT Probe

4.1 EC-PDT Probe Sterilization Method

As a general principle, the Japanese Sterility Assurance Level (SAL) requires achieving a level of better than 10^{-6}. SAL is a quantitative measure of the probability of there being one living micro-organism on the sterilized product, and 10^{-6} means that 1 product in 1 million sterilized products will have a living micro-organism on it. To assure SAL of better than 10^{-6}, the EC-PDT probes are sterilized using gamma radiation.

Due to the excellent penetrating power of gamma rays, finished products in sealed bags can be irradiated irrespective of product shape. Moreover, because gamma rays are part of the electromagnetic spectrum, there is no harmful residual material remaining in the target after irradiation.

Before sterilization with gamma rays, it is important to prevent bacterial adhesion during production. The production procedures taken by our company to achieve this are outlined below.

4.2 Manufacturing Procedure for Preventing Bacterial Adhesion

Production of sterile medical equipment required our company to first re-examine conventional production methods from basic principles.

Production in a clean room was thought to be best at the start, but devising the production methods described below facilitated effective use of an existing partitioned space in a simple clean room.

A triple partition design shown in Figure 7 was used for the medical equipment production facility with closed-filter ventilation system shown in Figure 8(a) to prevent ingress of microorganisms and insects. This design separated each of the parts storage shelving, production, and packaging areas; in addition, the parts acceptance and product shipping area was partitioned from the medical equipment production area using high-performance soft film. Moreover, as shown in Figure 8(b), an alcohol- dispensing sterilizer was positioned at the entrance to suppress bacterial ingress from outside carried on people and parts. Furthermore, as shown in Figure 8(c), clean benches were installed in the production work area to prevent ingress of airborne bacteria during work. Lastly, as shown in Figure 8(d), wipe-down of work areas with alcohol washes helped prevent bacterial growth.

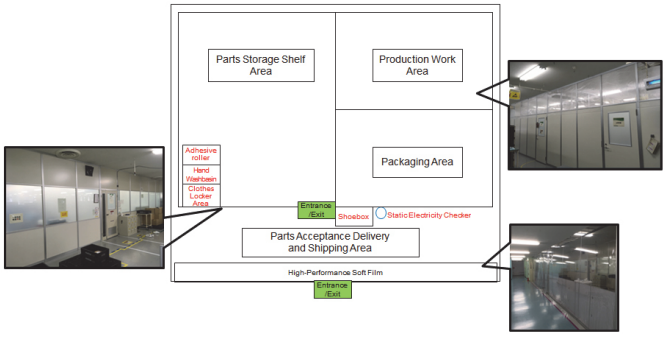

Figure 7 Medical Equipment Production Facility

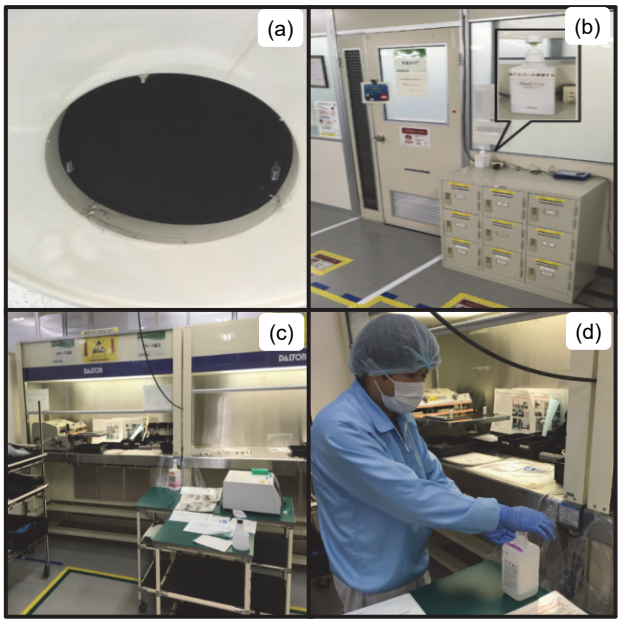

Figure 8 Medical Equipment Production Work

As a method to prevent bacterial adhesion during production work, a washbasin was installed in the medical equipment work area (Figure 9), which workers were obliged to use before starting work.

Figure 10 shows the other obligatory worker preparations. The procedure is: Change shoes (Figure 9(a)) → Wash hands (Figure 10(a)) → Change to lint-free clothes (Figure 10(b)), Wear mask (Figure 10(c)) → Wear cap (Figure 10(d)) → Wear gloves (Figure 10(e)) → Use cleaner to remove dust and lint (Figure 10(f)). Following these procedures maintains cleanliness, prevents dust generation, and prevents ingress of outside contaminants. In addition, a record of the results of these procedures was kept as evidence of worker quality assurance.

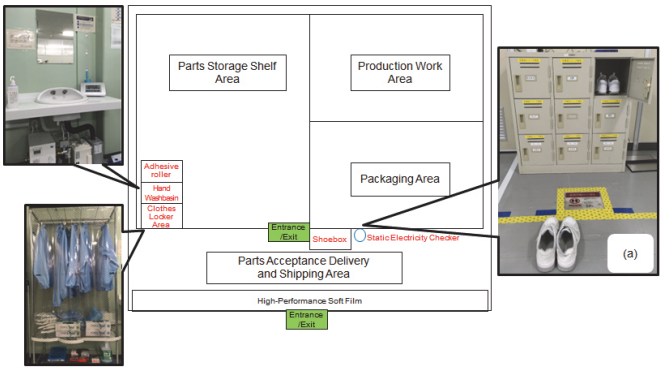

Figure 9 Medical Equipment Parts Shelf Area

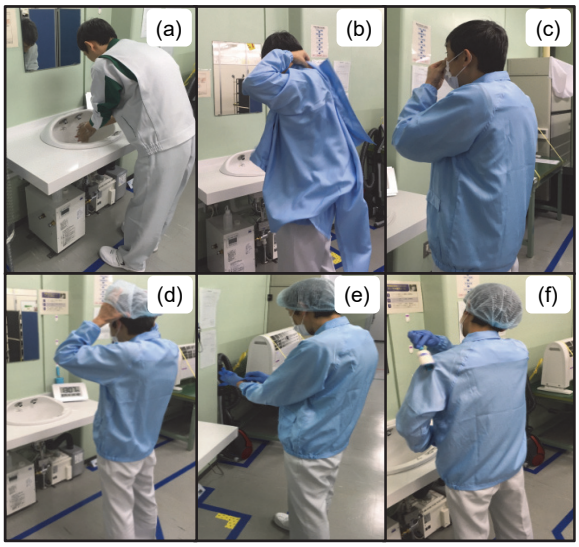

Figure 10 Worker Preparations

4.3 Managing Maintenance of Medical Equipment Production Environment

The most important part of manufacturing medical equipment to be careful about is related to bacteria (micro-organisms). Every square centimeter (1 cm^2) of the surface of a medical worker in a cleaned environment carries between 39,000 and 4,600,000 bacteria. Washing with soap reduces the bacterial count by 1/63 to 1/630, while sterilization with alcohol reduces the count by 1/3000. Endogenous skin bacteria are said to number between 100,000 and 1,000,000.

Bacteria cannot live and grow without water (humidity) and impurities (dirt and dust). Consequently, managed cleanliness assurance is important for medical equipment production environments. In addition to 24-hour air-conditioning management throughout the entire plant, a large air-conditioning unit (Figure 11) installed in the medical equipment production area helps reduce temperature and humidity. Moreover, installation of a plasma cluster generator emitting ions can maintain lower bacterial levels in the production environment by breaking down proteins in bacterial cell walls.

Figure 12 shows the results of temperature and humidity management in a medical equipment production facility. A standard temperature of 15° to 34°C is specified and the inspection location was managed to satisfy a temperature range condition of 20° ±15°C (JIS Z8703 Standard Temperature Conditions, Article 15). The standard maximum humidity is 85% and the lower limit at each temperature is

determined as shown in Figure 13 to hold the standard humidity in the range between the upper and lower limits.

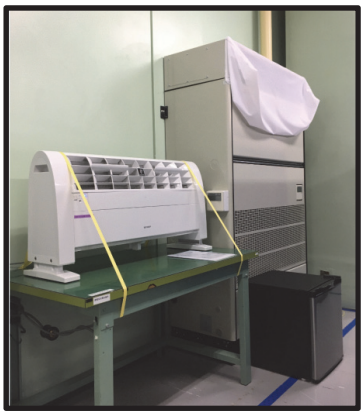

Figure 11 Large Air-Conditioning Unit

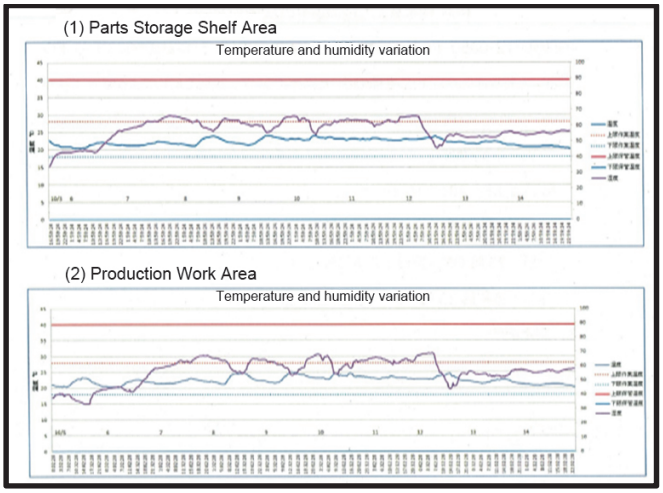

Figure 12 Temperature and Humidity Management of Medical Equipment Production Facility

Temperature ℃	Lower limit humidity %									
	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
15	54.6	54.3	54.0	53.7	53.4	53.1	52.8	52.5	52.3	52.0
16	51.7	51.4	51.1	50.8	50.5	50.3	50.0	49.7	49.4	49.2
17	48.9	48.6	48.3	48.1	47.8	47.5	47.2	47.0	46.7	46.4
18	46.2	45.9	45.6	45.4	45.1	44.9	44.6	44.3	44.1	43.8
19	43.6	43.3	43.1	42.8	42.6	42.3	42.1	41.8	41.6	41.3
20	41.1	40.8	40.6	40.3	40.1	39.9	39.6	39.4	39.2	38.9
21	38.7	38.5	38.2	38.0	37.8	37.5	37.3	37.1	36.8	36.4
22	36.4	36.2	36.0	35.7	35.5	35.3	35.1	34.9	34.6	34.2
23	34.2	34.0	33.8	33.6	33.4	33.2	33.0	32.8	32.6	32.1
24	32.1	31.9	31.7	31.5	31.3	31.2	31.0	30.8	30.6	30.2
25	30.2	30.0	29.8	29.6	29.4	29.2	29.0	28.9	28.7	28.5
26	28.3	28.1	28.0	27.8	27.6	27.4	27.2	27.1	26.9	26.7
27	26.6	26.4	26.2	26.1	25.9	25.7	25.6	25.4	25.2	25.1
28	24.9	24.7	24.6	24.4	24.3	24.1	24.0	23.8	23.7	23.5
29	23.4	23.2	23.1	22.9	22.8	22.6	22.5	22.3	22.2	22.1
30	21.9	21.8	21.6	21.5	21.4	21.2	21.1	20.8	20.8	20.7
31	20.6	20.4	20.3	20.2	20.1	19.9	19.8	19.6	19.6	19.5
32	19.3	19.2	19.1	19.0	18.9	18.8	18.7	18.4	18.4	18.3
33	18.2	18.1	18.0	17.9	17.8	17.7	17.6	17.4	17.4	17.3
34	17.2	—	—	—	—	—	—	—	—	—

Figure 13 Standard Humidity Reference Table

Manufacturing of medical equipment at the Anritsu plant was implemented by these facility and environment upgrades and environmental management.

5 Conclusion

This article outlines photodynamic therapy and Anritsu's work in medical equipment. At production of medical equipment, the key points are devising methods to prevent ingress of bacteria and organisms from outside into the production area, devising methods to prevent adherence of bacteria on medical equipment during production work, and managing assured cleanliness of the production environment.

Anritsu intends to continue providing sterile medical products by devising new production and management methods.

Authors

Koichi Akiyama
Business Originating Center

Takeshi Akimoto
Tohoku Anritsu Co., Ltd.

Publicly available