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Utilization of Clean Room for Radiopharmaceutical Kits Production

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Abstract. The radiopharmaceutical kit production facilities usually use a clean room with an aseptic process. Therefore, it is very important to conduct research on clean room utilization for the production of radiopharmaceutical kits. The data was taken from radiopharmaceutical product that produced at Center for Radioisotope and Radiopharmaceutical Technology (PTRR), National Nuclear Energy Agency (BATAN) from 2015 to 2018. The results indicate the use of clean room depends on the drying duration of the radiopharmaceutical kit. Almost all radiopharmaceutical kits are dried for two days such as MIBI, MDP, Ethambutol, MAA, and Tetrofosmin kits. There are only two kits that are dried for one day, DTPA and EDTMP kits. The ratio of monitoring of drying temperatures during the drying process of DTPA kit (one day) and MDP kit (two days) shows that in 2015 the freeze dryer still showed maximum performance compared to the next three years. The optimal utilization of clean room is in 2015 as much as 100% while in 2016, 2017 and 2018 the average utilization of clean room is around 66%. The production process frequency is the lowest in June, followed by January and December due to the maintenance schedule. The longer the process of drying radiopharmaceutical kits, the longer the clean room facilities operate. The production process of radiopharmaceutical kits in 2015 is the most optimal.

Keywords: Utilization, Clean room, Radiopharmaceutical kit, Freeze drying.

1. Introduction.

One of radiopharmaceuticals used in nuclear medicine is a radiopharmaceutical kit which is a pharmaceutical preparation in the form of lyophilized powder [1, 2]. In general, radiopharmaceutical kits are used for intravenous injection so that the preparation must meet sterile pharmaceutical requirements. The sterile production process is divided into two, namely terminal sterilization and aseptic process [3-5]. The clean room is a facility that is controlled for particle contamination and microbiology and can be used for aseptic production processes [6].

The production process of radiopharmaceutical kits is carried out in a clean room. Clean room has a level of cleanliness, according to their use. Based on good manufacturing practice (GMP), the clean room class is divided into three, namely class A, B, and C. The process of filling and lyophilizing the product is done in class A [7]. The radiopharmaceutical kit was lyophilized in freeze dryer, this method is chosen for chemical substances that are not heat resistant [8, 9]. The radiopharmaceutical



product is not susceptible against the heating process because the formula contains reductors [10]. Radiopharmaceutical kits have different production times, some are not dried, and some are one day or two days dried. This depends on the characteristic of active ingredient in each radiopharmaceutical formula [2, 11].

Center for Radioisotope and Radiopharmaceutical Technology (PTRR), National Nuclear Energy Agency (BATAN) also has a GMP certificate that can be used for the production of commercial products by PT. Kimia Farma. Recapitulation data is needed to maintain the service quality of radiopharmaceutical kit production. Therefore, research on clean room utilization analysis for the production of radiopharmaceutical kits must be carried out.

The purpose of this study is to find out whether the clean room in PTRR has been utilized to the maximum extent possible or is there a way to improve the performance of clean room so as to produce better commercially and research and development (R & D) products.

2. Methods

2.1. Data collection for drying radiopharmaceutical kits

Drying temperature data using a freeze dryer (Labconco) are taken from the freeze dryer logbook. The operational capacity is 125 vials per batch of production. The radiopharmaceutical kit sample was diethylene triamine penta-acetic acid (DTPA) kit and methylene diphosphonate (MDP) kit which was dried for one and two days respectively. Temperature data displayed in the graph which is continuously displayed every hour until the process ends.

2.2. Analysis of utilization of clean room based on product

Data were taken from the radiopharmaceutical kit process from 2015 to 2018 at the PTRR-BATAN. The data is classified into three groups such as commercial radiopharmaceutical kits, R & D radiopharmaceutical kits and product of dummy validation (media fill). Data was presented in the form of bar charts to describe the trends in the annual radiopharmaceutical kit production.

2.3. Analysis of utilization of clean room based on production schedules

The radiopharmaceutical kit process can be held for a maximum of three times a month. However, clean room has limits on their use. Every two times year maintenance needs to be done. Maintenance schedules are usually in June and December. Production data of radiopharmaceutical kits will be presented in the form of bar charts per month of production to see the efficiency of utilizing clean room.

3. Results and Discussion

In general, production in the pharmaceutical industry is supported by Production and R & D Department. In BATAN three radiopharmaceutical kits can be produced commercially in collaboration with PT. Kimia Farma and more than four radiopharmaceutical kits are still in the process of optimization. Commercial products include methylene diphosphonate (MDP) kits, diethylene triamine penta-acetic acid (DTPA), and methoxy isobutyl isonitrile (MIBI) while some radiopharmaceutical kits are still in development stages as ethambutol, macroaggregates (MAA), tetrofosmin, and ethylenediamine tetramethylene phosphonic acid (EDTMP) kits. There is also a media fill validation that is used to ensure that the aseptic production process normally carried out does not cause contamination of the product. The use of clean room in each radiopharmaceutical kit production can be seen in Table 1.

In table 1 shows the radiopharmaceutical kit process varies in the drying process of one day and two days. The media fill was using freeze dryer but not operated completely so that the media fill process is only one day. Tetrofosmin kits are also formulated with two variations, liquid form and dry powder form. For liquid tetrofosmin kit, clean room utilization is only one day because it does not require drying, while dry tetrofosmin kit requires two days of drying with three days of utilization of a

clean room. Almost all radiopharmaceutical kits are dried for two days and for radiopharmaceutical kits that have simple formulas and do not have fillers such as DTPA and EDTMP only require one day drying process.

The process of drying the kits using a freeze dryer can take one to two days. Drying starts with the setting of $-40\text{ }^{\circ}\text{C}$ for several hours, after primary drying the temperature is increased gradually to $0\text{ }^{\circ}\text{C}$ and finally $15\text{ }^{\circ}\text{C}$ which is called secondary drying phase. The drying process is shown in Figure 1 for DTPA kits and Figure 2 for MDP kits with duration of one day and two days respectively.

Table 1. Data on utilization of freeze dryer and clean room.

Type of product	Name of product	Duration of use of freeze dryer	duration of use of clean room
Commercial	MDP Kit	2 days	3 days
	DTPA Kit	1 day	2 days
	MIBI Kit	2 days	3 days
R & D	Ethambutol Kit	2 days	3 days
	MAA Kit	2 days	3 days
	Tetrofosmin Dry Kit	2 days	3 days
	Tetrofosmin Liquid Kit	0 day	1 day
	EDTMP Kit	1 day	2 days
	Others	1 – 2 days	2 – 3 days
Dummy product validation	Media fill	0 day	1 day

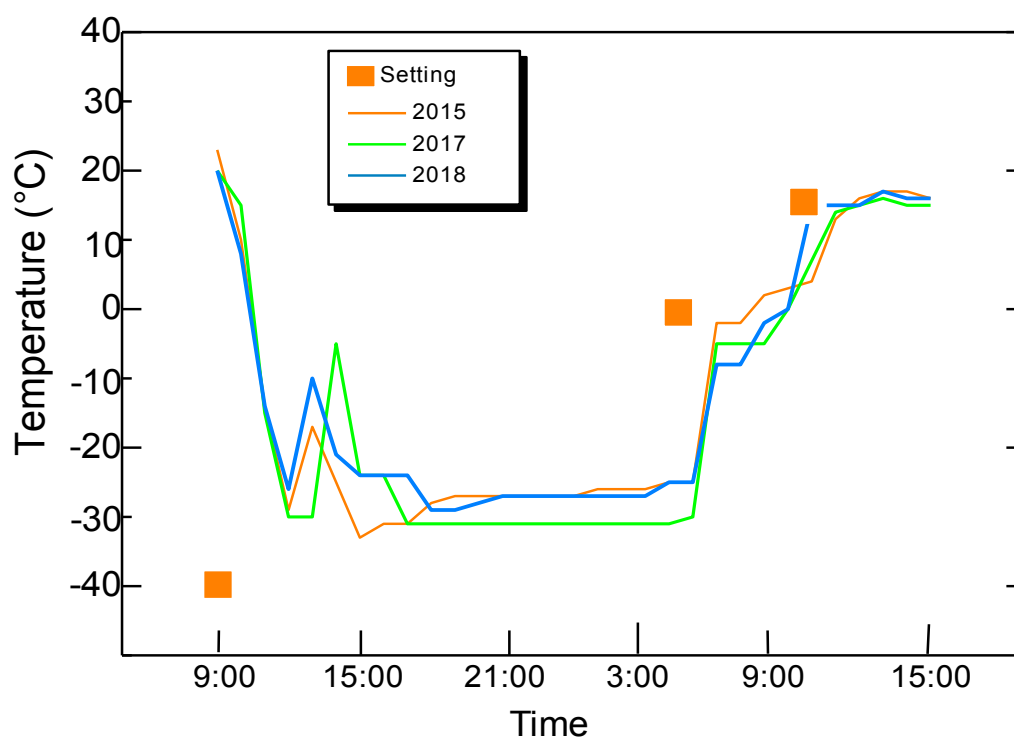


Figure 1. Temperature monitoring during the production process of a DTPA kit (drying in one day).

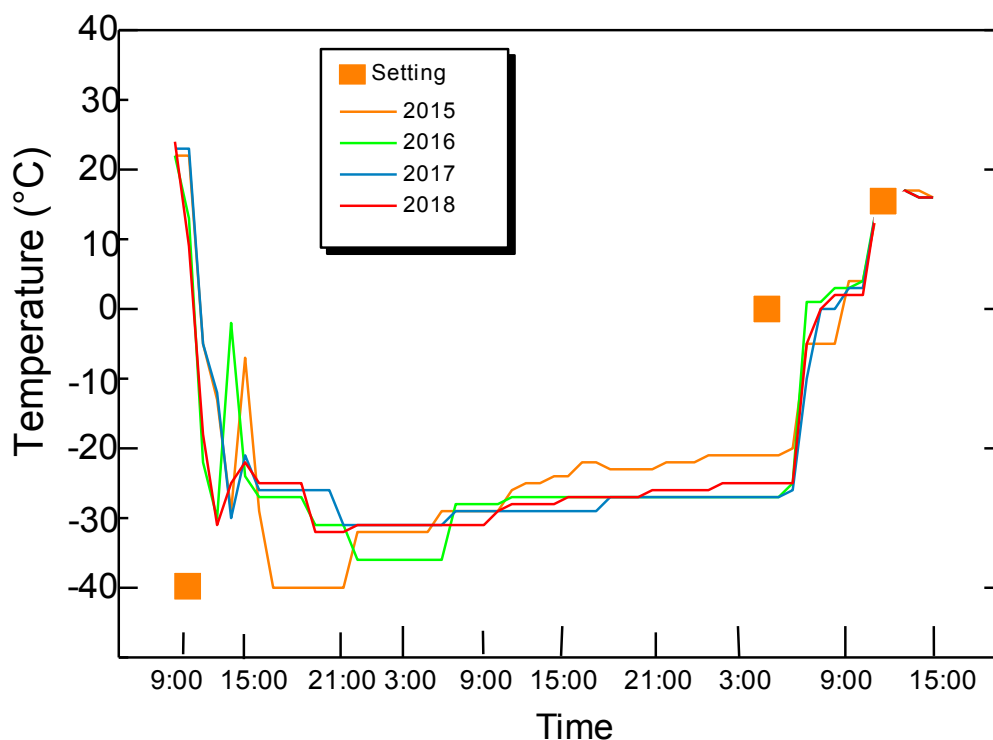


Figure 2. Temperature monitoring during the production process of a MDP kit (drying in two days).

Figure 1 shows continuous temperature monitoring of the DTPA kit process with one day drying time and Figure 2 shows the MDP kit process with a drying time of two days. In 2016, DTPA kits was not produced so it was excluded in the diagram. The production process is usually carried out at 10:00 with the initial temperature on the tray of around 20 to 23 °C then set to -40 °C at 12:00 to 14:00 there is a peak that rises from -30 to -5 °C. This happens because of the process of entering the product into the freeze dryer. The product was loaded into freeze dryer when the tray temperature reached around -30 °C. Then, it was frozen at -40 °C during which the vacuum was applied. In 2015, the performance of the freeze dryer was still very good so that the real temperature reached the temperature setting at each point (-40, 0, and 15 °C) compared to 2016, 2017 and 2018. In 2015, the tray temperature reached -40 °C during the drying process of MDP kits, while in DTPA kits the lowest temperature was below -30 °C. The critical point of drying the kits is at the optimal temperature of -40 °C and the vacuum condition of the freeze dryer itself. After primary drying process the product was undergoing secondary drying with the purpose of evaporating remaining water on the surface of the sample. Therefore, the temperature is increased gradually to 0 then to 15 °C. The temperature of 0 °C is set at 05:00 AM and 15 °C is set at 10:00 AM and the kits are ready to be taken out at 12:00 AM.

The production process of radiopharmaceutical kits has similarities with the sterile production process. In PTRR, there are two freeze dryers to be used for commercial production and R & D purpose. In one month three processes can be carried out. Assuming twice maintenance schedules in one year, the production process can be carried out a maximum of 30 times per year. Maximum utilization of clean room was carried out in 2015 with a total process of 100%. However, it decreased in 2016, 2017, and 2018 with a percentage of 63%, 70%, and 67% respectively.

Furthermore, the MDP kit process was consistent with the number of four to five times per year. The frequency of DTPA kit production decreased from five in 2015 to zero in 2016, this is because of low market demand for DTPA kits. However, the DTPA kit is again produced in 2017 and 2018. In addition, the MIBI kit was consistently produced two to four times per year.

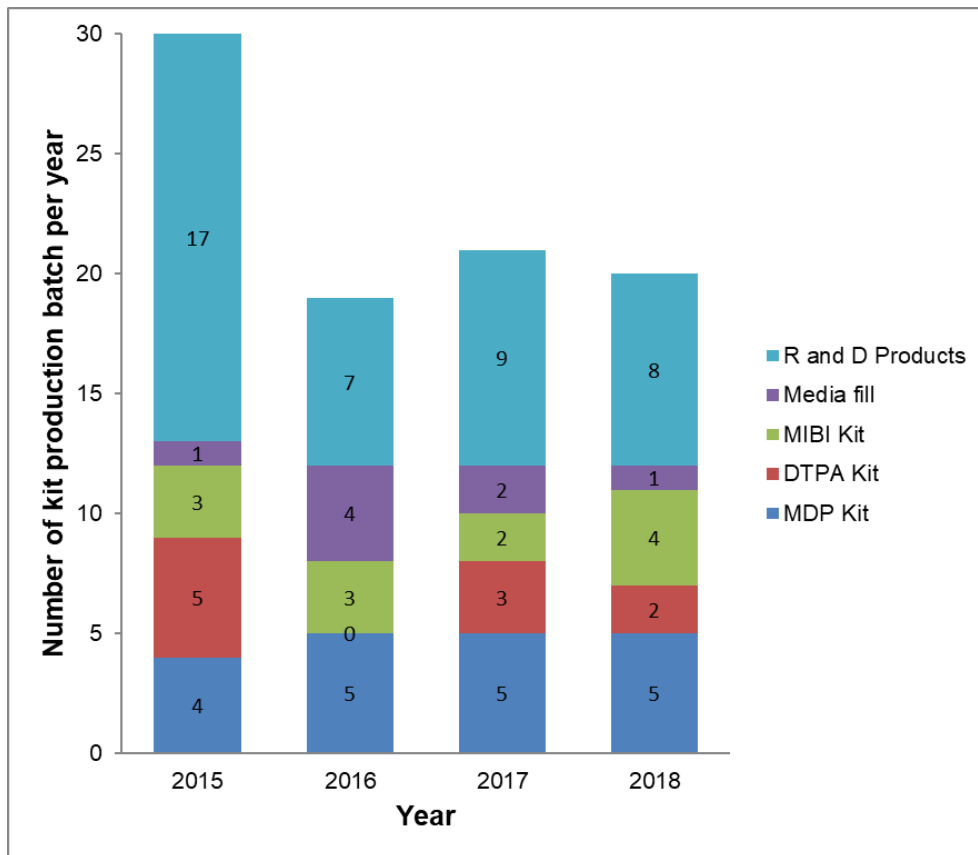


Figure 3. Utilization of clean room based on production batch within four years (2015 to 2018).

Clean room facilities are basically supported by very complex systems such as heating, ventilation, and air conditioning (HVAC). Requirements regarding temperatures of around 16 to 25 °C, relative humidity (RH) of about 45 to 55%, the difference in pressure between spaces is around 10 to 15 pa. Every two times a year maintenance needs to be done so that the clean room condition remains optimum. In Figure 4, the frequency of the production process was minimum in June, because this month coincides with the maintenance schedule.

In addition, the maintenance schedule was also held in January or December. However, this pattern does not occur every year as an example in 2015 maintenance of facilities is only carried out once in June but in 2016 two treatments were carried out, in June and November. In 2017, there was also a one-time treatment in March to April as a consequence in 2018 maintenance was done twice in May and December. Regularly, damage to a clean room facility occurs in the part of filter, HVAC, and air pressure system. The type of maintenance carried out can be divided into routine and emergency maintenance. Emergency maintenance is carried out when unpredictable damage occurs while routine maintenance is a scheduled agenda. The total duration of maintenance depends on the type of damage and can reach two months. In addition, the use of clean room is also hampered by the presence of external factors such as raw materials that are not available or production equipment that is not calibrated. In this case the production and maintenance schedule must be arranged each year so that the production process can run well.

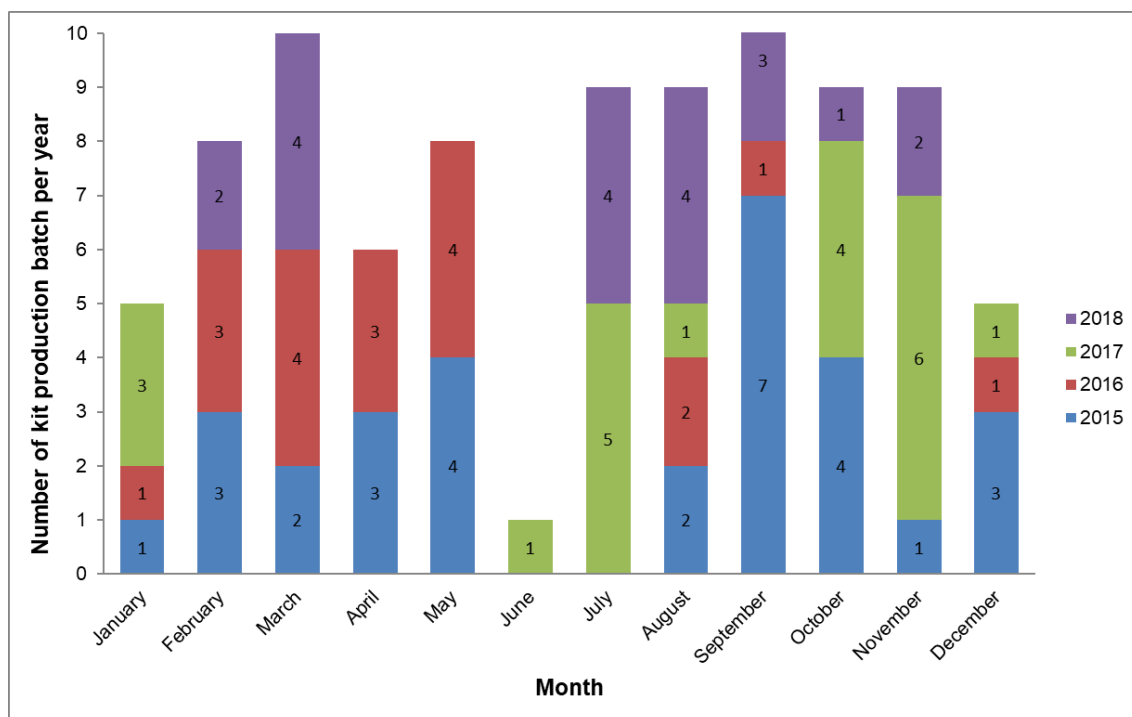


Figure 4. Analysis of the use of clean room based on time per month

4. Conclusion

The most optimal utilization of clean room was in 2015 as much as 100% while in 2016, 2017 and 2018 the average utilization of clean room was around 66%. The frequency of production process was the lowest in June, followed by January and December due to maintenance schedule. This maintenance schedule is very important in determining whether environmental parameters such as temperature, relative humidity, and differential pressure between spaces, number of particles and the number of microbiology meet GMP requirements so that the production process can be carried out.

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