Indonesia International Institute for Life Sciences

ENRICHMENT PROGRAM REPORT

Water for Injection Hold Time Study in Room Temperature

STUDY PROGRAM
Biotechnology

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INTERNSHIP REPORT
WATER FOR INJECTION HOLD TIME STUDY AT ROOM TEMPERATURE

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CERTIFICATE OF APPROVAL

Certificate of Approval

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ABSTRACT

During the internship, the main project done is the Water for injection hold time study at room temperature. Water for injection is a type of pure water used in pharmaceutical production that has been treated using distillation. Water for injection is used for cleaning equipment, mixing solutions, and validating cleaning. The study aims to investigate the condition of water for injection for a period of 2 weeks to determine the hold time of water for injection and monitor the various parameters as described by Farmakope Indonesia. The six parameters described as appearance, pH, conductivity, Total organic Carbon (TOC), bioburden, and endotoxin. The results of the project revealed that the condition of the water for injection overall is kept stable throughout the two weeks using the laminar air flow and the sterile gloves used in sampling. However, vapors of alcohol used in the room to sterilize equipment results in increasing levels of TOC to build up. This study helps the company to keep up with their productivity in the events that water for injection in unavailable for a period of time

Keywords: Water for injection; hold time; Total organic Carbon (TOC)

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LIST OF ABBREVIATIONS

KGM : Pt Kalbio Global Medika
PW : Purified Water
WFI : Water for Injection
CIP : Clean in Place
CLV : Cleaning validation
TOC : Total Organic Carbon
TC : Total Carbon
IC : Inorganic Carbon
MCD : Sievers Membrane Conductometric method
TAMC : Total Aerobic Microbial Count
TYMC : Total Combined Yeast and Mold Count
LAL : Limulus Amebocyte Lysate
MVD : Maximum Valid Diffusion
USP : United States of America’s pharmacopeia

I. INTRODUCTION

I.1. Brief History of PT Kalbio Global Medika

The Kalbe group, or Kalbe Farma is a company started by K.L. Tjoen, Theresia H. Setiady, Khouw Lip Swan, Khouw Lip Boen (Also Known As: Dr. Boenyamin Setiawan), Maria Karmila, and F. Bing Aryanto, six siblings who wanted to boost the pharmaceutical industry on September 10 1966. PT Kalbio Global Medika is a branch company of PT Kalbe Farma specializing in the production of different pharmaceutical products such as human erythropoietin (hEPO). First established in 2014 and inaugurated in 2018 by the president of Indonesia, Joko Widodo, PT Kalbio Global Medika has been a leading healthcare provider for Indonesia and south-east asia.

I.2. Vision and Mission

PT Kalbio Global Medika (KGM) has a vision to be the best CMO and CDMO in the region, driven by Quality, Innovation and Operational Excellence. This company has mission to improve health for a better life by providing high quality and accessible biopharmaceutical products

I.3. Main activities of PT Kalbio Global Medika

KGM is a pharmaceutical company specialized in the production of different pharmaceutical products through the development and optimization of mammalian cell culture production. The main products of KGM include different kinds of protein and monoclonal antibodies. In addition to protein production, KGM is involved in the fill and finish process, producing millions of syringes, cartridges, and vials, as well as the packaging process. Other than the production of their products, they offer different services starting from cell storage to full release. QC toll services are also offered for companies that need it. KGM uses an eco-friendly facility with solar panels and a chiller plant automation system to reduce emissions of greenhouse gasses.

I.4. Organizational structure

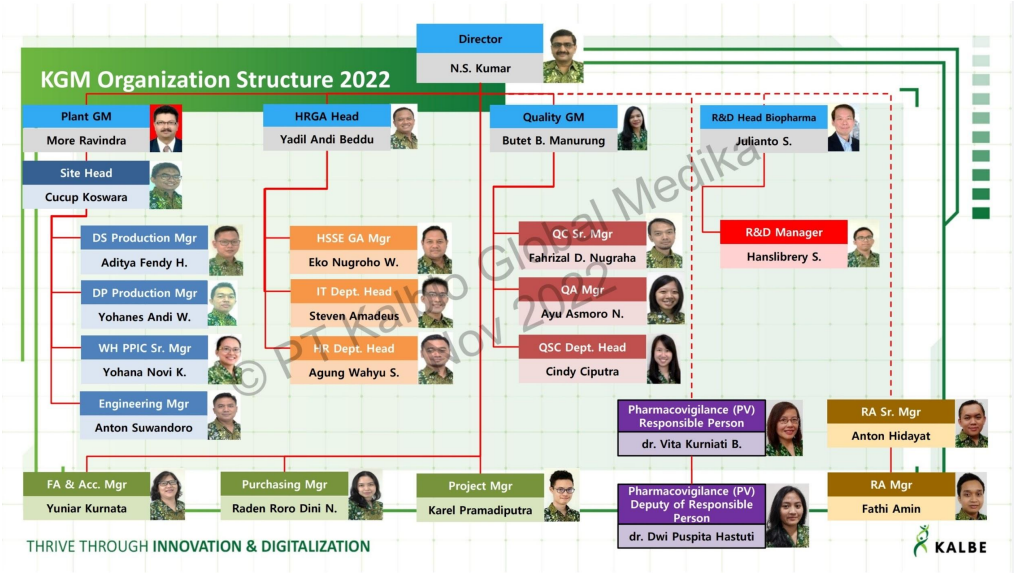

Figure 1. Kalbio Organizational Structure

I.5. Student's department

I am involved in the production department of KGM, specifically the upstream production while supporting the downstream production department. The Upstream production of KGM is focused on the maintenance of mammalian cell cultures including inoculation, storage, and harvesting of cells. Using state-of-the-art equipment and quality facilities to house the different cultures. In addition, the production department is involved in cleaning and sterilizing different equipment. The harvested cells are given to the downstream production department to be processed.

II. INTERNSHIP ACTIVITIES

II.1. working conditions

During the internship, the typical work day lasts from 8 am to 5 pm with an hour lunch break from 12 pm to 1 pm. On Fridays, the break time is extended to an hour and a half, starting at 11:30 am to 1 pm. Work is done in the office and in the production area. Lunch was provided every break time. Water is provided in the office break room alongside basic consumption like coffee. In the office, the work consists of clerical work, including filling in forms, entering data into databases, and preparing proposals. Office work is done in cubicles and work is assigned by field supervisors. Computers are not prepared for interns and personal laptops are used. In the production facilities, the work is done in grade D areas and grade C areas. To enter grade D areas, personnel must change to a prepared apparel and wear a different mask and hair net. A new pair of socks must be worn before entering the changing room. After changing, special shoes and gloves are worn and work can be done. Work in the production facility includes cell harvest and inoculation, washing equipment, and preparing equipment to be used later.

II.2. Internship tasks and Experience gained

During the internship, I helped out in the production process which includes cell harvest and inoculation. Cell harvest and inoculation is done in a grade C area. To enter a grade C area, personnel must wear a special jumpsuit, shoe covers, and another hair net. The cell harvesting and cell inoculation uses a machine known as the cellmate. The cellmate is a machine consisting of a BSC with a robotic arm operating inside. The robotic hands automatically take bottles from the input conveyer belt and dispense fluids inside. During harvesting, trypsin is dispensed inside to stop cells from adhering to the bottle walls and allowing them to be harvested. It is incubated for 300 seconds, as any more may result in the cells clumping. Five bottles is the optimal number of bottles that can be processed at a time and adding more may result in the machine not being fast enough to pour out the trypsin on ready bottles resulting in clumping. Personnels must wipe the bottles with lint-free wipes soaked in 70% alcohol to sterilize them before loading them into the input conveyer belt. A finished bottle is placed in the output conveyer belt and personnel must collect them and decontaminate them. Decontaminating is done by filling bottles with water for injection and shaking the bottles. water for injection lyses the cells making it clean. After decontaminating, the bottles are thrown away. Cell inoculation is done after cell harvesting. New bottles are sterilized and placed in the input conveyer belt, where the machine fills it with harvested cells and new medium. The bottles will be labeled and placed on the rolling racks and the racks are pushed back to the storage rooms.

For cleaning, small parts are rinsed with purified water (PW) 3 times. Each time, the personnel must make sure that water has entered every gap and crevasses in the piece of equipment. A chemical wash with NaOH is done before a final three since with water for injection. Once it is done, a rinse sample is done by getting a clean basin and submerging all the small parts inside it in water for injection. The water is poured into the sample bottles and sealed quickly. The bottles are labeled and brought to the QC department for testing. Larger objects like 50L bottles are washed in the dedicated dishwasher and are not tested. Once the results return and the items are cleared, it is then brought to the sterilization room to be autoclaved. Once autoclaved, it is sealed inside the wipak to be transported to the production rooms.

In this internship I am involved in a project that investigates the condition of water for injection for a period of 4 weeks to determine the hold time of water for injection and monitor the various parameters as described on Farmakope Indonesia. I gained experience about how to determine six parameters described as appearance, pH, conductivity, Total organic Carbon, bioburden, and endotoxin that are the quality parameters for water for injection.

II.3. Compare between theory and practice

A major difference between what is learned on campus and in the company is the procedures of cell culturing. In the production process, hundreds of bottles are passaged every passaging process, compared to the smaller scale passaging in the labs during lectures. As such, machines are used to facilitate the passaging process. Machines harvest cells and culture them again while on campus, the passaging process is done by hand. Another main difference is the aseptic techniques. Due to the greater impact in cases of contamination, sterility is important. Entering the production facility requires using their gowning and abandoning most personal belongings. Compared to the lab in which lab coat and goggles sufficed. In addition, learning about intricate procedures for using various equipment is necessary to keep the sterility intact and carefully following the procedures is necessary to stop contamination.

II.4. Difficulties encountered and how you overcome them

The main difficulty I have faced in my workplace is shifting from online lessons to a workplace schedule of 8 am to 5 pm. Compared to working office hours, university classes have more break time and lasts for a shorter time, which gives more time to rest and recover strength. In addition, the atmosphere of the classes is often more relaxed. In the office, moment to moment activity is important and has to be kept up for the entirety of the work hour, and as such, can be more mentally demanding compared to the courses. As a result, I am often too exhausted when I go back to do other activities. In addition, the longer work hours gives less time to do other activities at home. As such, often times,

To overcome the difficulties, planning a schedule ahead of time for the day. By taking time to decide on what tasks to do for the day, I can feel more productive at work. Scheduling time at home helps with maximizing time to unwind, making sure to not waste the time at home to give as much free time as possible. In addition, getting enough sleep is important to not feel exhausted at work and at home.

III. PROJECT DESCRIPTION

III.1.1. Project background

A holding time is defined as the amount of time that has passed after a sample has been collected up to the moment the sample is processed or analyzed. An analytical holding time refers to the maximum holding time a sample can be stored for until it is no longer fit for analysis or usage due to alterations to its chemical and physical properties which may compromise its integrity (McCoy *et al,* 2012). Alterations to properties can be caused by contaminations to the materials which makes them unable to be used. Several sources of contamination are airborne microbes and microbes carried by personnels.

Water for injection is an important material in the production process for different purposes, including mixing solutions, cleaning and decontaminating equipment, and validating the cleaning after the cleaning process. Various equipment in the production process employs CIP to clean the internal parts of the machines. After the CIP process, CLV is done to ensure that the cleaning is thorough by collecting rinse samples of the equipment and testing the parameters compared to water for injection specifications (Goyal *et al,* 2016). The CLV process is necessary to ensure the quality of the product to prevent possible contamination. Contamination in pharmaceutical products will be catastrophic for both the company and the consumer. In order to evaluate whether the water can be considered as water for injection. A series of parameters must be measured and if the water is within acceptable range, it can be considered as water for injection. The parameters included: pH, electrical conductivity, bioburden, Total organic carbon concentration, and endotoxin.

Water for injection is produced and stored in the storage facility and piped to the production facility for use. However, there are moments in which water for injection is unavailable for use, such as during maintenance of the filtration and storage facilities, production can not proceed. To counteract this, water for injection is taken beforehand and stored in carboy bottles until it is needed for the processes. However, storing water for injection in room temperature can cause alterations to the properties of the water and causes products produced using the water to be unfit for consumption. As such a study must be conducted to find the hold time of water for injection to ensure that in situations where water for injection is unavailable, production can resume safely by finding the amount of time the water can be stored for.

III.1.2. Scope

Study is done based on the six parameters of water for injection, as described by Farmakope Indonesia. The six parameters include: pH, conductivity, TOC, bioburden, Endotoxin, and appearance. Tests are done to determine the current condition of the stored water for injection to determine whether the water for injection is still fit for usage.

III.1.3. Objectives

Study is done to determine the analytical holding time of water for injection samples based on the six main parameters: pH, conductivity, total organic carbon (TOC), bioburden, endotoxin, and appearance.

III.1.4. Problems on the challenges faced by the section/host institution viewed from the perspective of science

The main challenges faced by the institution are that storing water for injection in room temperature before use may cause the water to be contaminated and therefore unfit to use for production. Aerobic microbes such as *Pseudomonas* are able to grow in the water, even under laminar air flow. Using sterilizing agents may alter the properties of the water, such as ethanol increasing the TOC levels and chlorine potentially damaging the products. Ozone is utilized to sterilize the water, but it is difficult to sterilize water in such low quantities outside of the water processing plant. Storing water in low temperature may extend the hold time significantly, but will use up a lot of energy, and due to the low frequency of such a situation happening, purchasing in a large freezer may not be a worthwhile investment.

III.2. Methodology

The study is done in multiple runs. water for injection is filled into a sterile carboy bottle and placed in the facilities. The water is sampled three times every week with 2 weeks each run. The bottles are sampled in laminar air flow to ensure no contamination during the process. Every sampling point, a personnel must wear a pair of sterile gloves and sleeves and use a serological pipette to collect samples to keep the integrity of the samples. Six main parameters are measured: pH, conductivity, TOC, bioburden, endotoxin, and appearance. Sampling is done using serological pipette to ensure the integrity of the sample. The samples are labeled and sent for analysis. The measurements are then compared to the Farmakope Indonesia standard below (Air untuk Injeksi, 2020).

Table 1 Acceptance criteria for water for injection based on Farmakope Indonesia

Parameter	Acceptance criteria
pH	5-7
TOC	<500 ppb
Bioburden	<10 CFU/100 mL
Endotoxin	<0.25 EU/mL
Conductivity	Refer to table 1 and table 2 in appendices
Appearance	Clear, colorless, and odorless

III.2.1. Appearance, pH, and Conductivity

The appearance of the water for injection must be assessed first before other analysis. water for injection should be colorless and clear. pH is measured often times in conjunction Any sort of discoloration in the water will cause the water for injection to be considered unusable. Measurement of pH is done in tandem with conductivity measurement due to their similar nature. Using a pH probe, measurements of the water for injection pH are done before conductivity measurements. Conductivity measurements are done in three stages: Temperature based, at room temperature, and pH-based. In temperature based measurements, the temperature of the sample is measured before

using a pair of electrodes to measure the conductivity until the conductivity stabilizes. If the first stage results in failure, the second stage is done. Second stage uses a water bath to heat up the sample to 25±1°C and keep the temperature at that degree during measurement. Third stage is done by measuring the pH first before measuring the conductivity. If the sample were to fail for all three stages, the sample is considered failed. pH measurements are done using a pH meter. It may be done in tandem with Conductivity measurements if stage 3 conductivity measurements are done (Water Conductivity, 2012).

III.2.2. Total Organic Carbon (TOC)

TOC is measured through the Sievers Membrane Conductometric Method (MCD). MCD is done by first purging the water from inorganic carbon compounds, carbonates, bicarbonates, and atmospheric CO_2 by reducing pH using acid. The resulting process produces CO_2 which is moved to the detection chamber through a CO_2 permeable membrane. This is measured as inorganic carbon (IC). Once the IC has been purged, the organic carbon compounds are oxidized and broken down to CO_2. The CO_2 is again moved to the detection chamber through a CO_2 permeable membrane. In the detection chamber is currently the carbon dioxide produced by inorganic and organic compounds, which is considered as total carbon (TC). To get TOC, TC is subtracted by the IC to get the amount of TOC (Shetty & Goyal, 2022).

III.2.3. Bioburden

Bioburden is measured through the membrane filtration test. Membrane filtration test is commonly used to test water quality. The test is divided into two, Total Aerobic Microbial Count (TAMC) and Total Yeast and Mold Count (TYMC). To perform both tests, the water for injection sample is drawn through a filter paper using a vacuum pump. The filters are then incubated in Trypticase Soy Agar (TSA) and Sabouraud Dextrose Agar (SDA) medium respectively for 5-7 days. The Colonies are counted and the results of both are averaged to find the number of colony forming unit (CFU) per mL (Ganiyu *et al*, 2015)

III.2.4. Endotoxin

Endotoxin are toxic complexes which are produced in the cell walls of gram-negative bacteria. Endotoxin produces an immune reaction when interacting with the polysaccharide receptors of a white blood cell, which results in inflammation and fever for the patient. The main method used to detect endotoxin is the gel clot test. Gel clot test is a qualitative test done using LAL (limulus amebocyte lysate) as a reagent, which is taken from horseshoe crabs (*Limulus polyphemus*). The LAL reagent is mixed with lysate reagent water to create the initial reagent test. The sensitivity of the test is often given by the manufacturer, but can be measured by testing on known concentrations. Control stock endotoxin is made by creating a 1 EU/mL endotoxin solution and using serial dilution to create a series of controls with each stock half the concentration of the previous stock. Before measurement, maximum valid dilution is calculated to ensure when diluting the water sample, the endotoxin concentration in the water does not drop below the measurement threshold. Maximum valid dilution is calculated using the following equation: MVD = (Endotoxin limit X Sample concentration)/Test sensitivity. The lysate reagent is mixed with the water sample and the control stock endotoxin and incubated for 60 minutes in a 37 °C water bath. The tubes are then inverted and if the gel slides down the tube, the gel has not clotted and is considered negative. If the gel remains in the tube, the result is positive (Hashmi & Thakur, 2019).

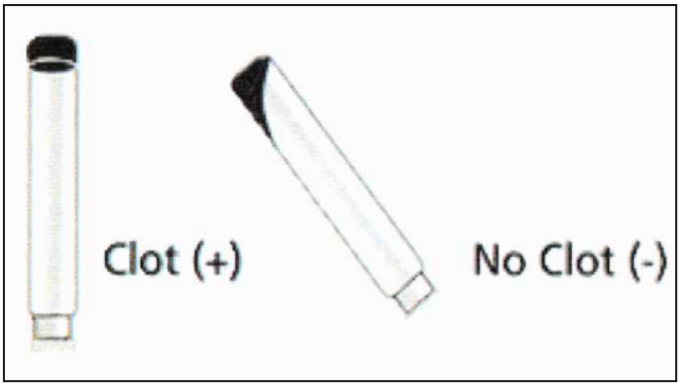

Figure 2. Gel clot results

III.3. Result and discussion

In this internship, I have investigated six parameters of water for injection (water for injection). The six parameters include: appearance, pH, conductivity, TOC, bioburden, and endotoxin. Tests are done to determine the current condition of the stored water for injection to determine whether the water for injection is still fit for usage during two weeks of storage. The following is the results of the appearance evaluation of the water sample (Table 2). The results from observation shows that the samples of water for injection has colorless and clear that meet the requirements of Farmakope Indonesia standards and all samples pass the appearance parameters during 2 weeks of storage

Table 2. Appearance evaluation of the water sample

Run	Day	Pass/Fail
1	0	Pass
	2	Pass
	4	Pass
	7	Pass
	9	Pass
	11	Pass
2	0	Pass
	2	Pass
	4	Pass
	7	Pass
	9	Pass
	11	Pass
3	0	Pass
	2	Pass
	4	Pass
	7	Pass
	9	Pass
	11	Pass

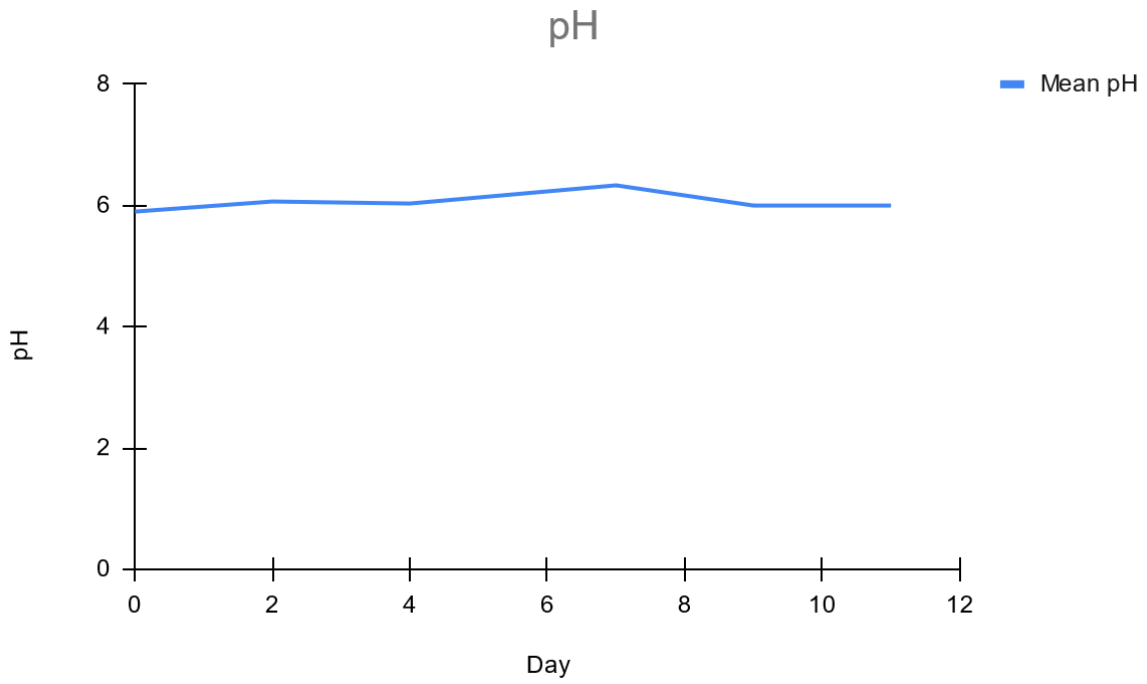

Figure 3. pH

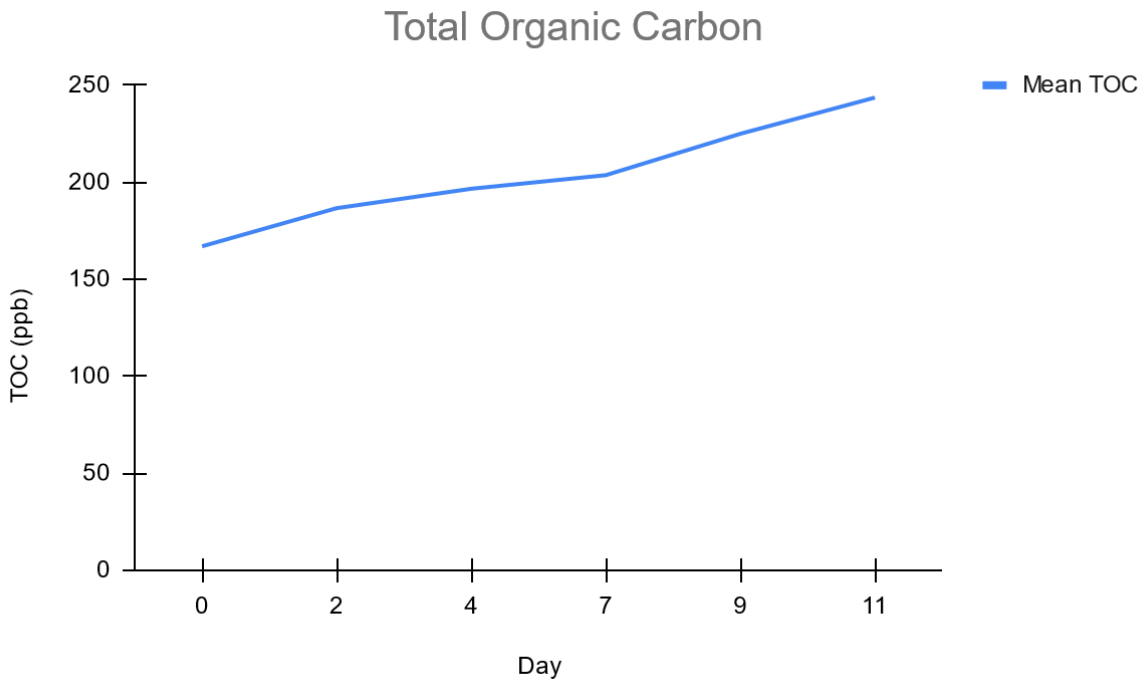

Figure 4. Conductivity

The conductivity measurements are only done up to the first stage as the results are deemed appropriate after first stage testing. As a result, the conductivity measurements are done in different temperatures, which affects the conductivity measurements. To draw a solid conclusion, the conductivity data is corrected to an approximation of measurement if the measurement is done at 25℃ based on the study conducted by McCleskey (2013). For conversion, the temperature coefficient of change is calculated using the standard of conductivity at 20 ℃ and 25 ℃. The formula used is $\alpha_{\theta,25} = \frac{K_\theta - K_{25} \times 100}{K_{25}(\theta - 25)}$. K represents the conductivity at the specified temperature and θ represents the temperature at which the conductivity is measured. The resulting temperature coefficient of change being 40/11. To perform correction, the formula used is $K_{25} = \frac{K_\theta}{1+(\theta-25)(\alpha_{\theta,25}/100)}$. Results may differ slightly in real testing if the temperature of the water is increased to 25℃ in a water bath, but the approximation of correction gives a method to standardize the data across different temperatures.

Based on the analysis results, both conductivity and pH measurements fluctuate within the acceptable range (Figure 2 and 3), meeting the Farmakope Indonesia standards. As such, inorganic contaminants are considered to not be a factor limiting the hold time. Conductivity measurement of water for injection is done to measure the amount of ionic and inorganic materials in the water for injection (*Indicators: Conductivity*, 2022). Pure water has a baseline conductivity that changes based on temperature and dissolved ions. In order to limit the detection to detecting only inorganic pollutants, a baseline based on temperature and pH is established, as outlined in appendices (by table 1 and table 2). By using this metric, conductivity tests are used to detect foreign inorganic ions such as chlorides, phosphates, and nitrates which may bring adverse effects on people consuming them. Chlorides affect cardiovascular health (Hoque et al., 2018). High levels of nitrates are believed to be carcinogenic in humans and result in enlargement of thyroid glands and increased risk of diabetes mellitus (Parvizishad et al., 2017). High levels of phosphate may result in increased risk of kidney failure (Komaba & Fukagawa, 2016). In addition, heavy metals can also be detected which are fatal to consume (Engwa *et al*, 2019). Conductivity levels that are too high indicate a high amount of inorganic ions, which is dangerous to consume and damages products if used in production.

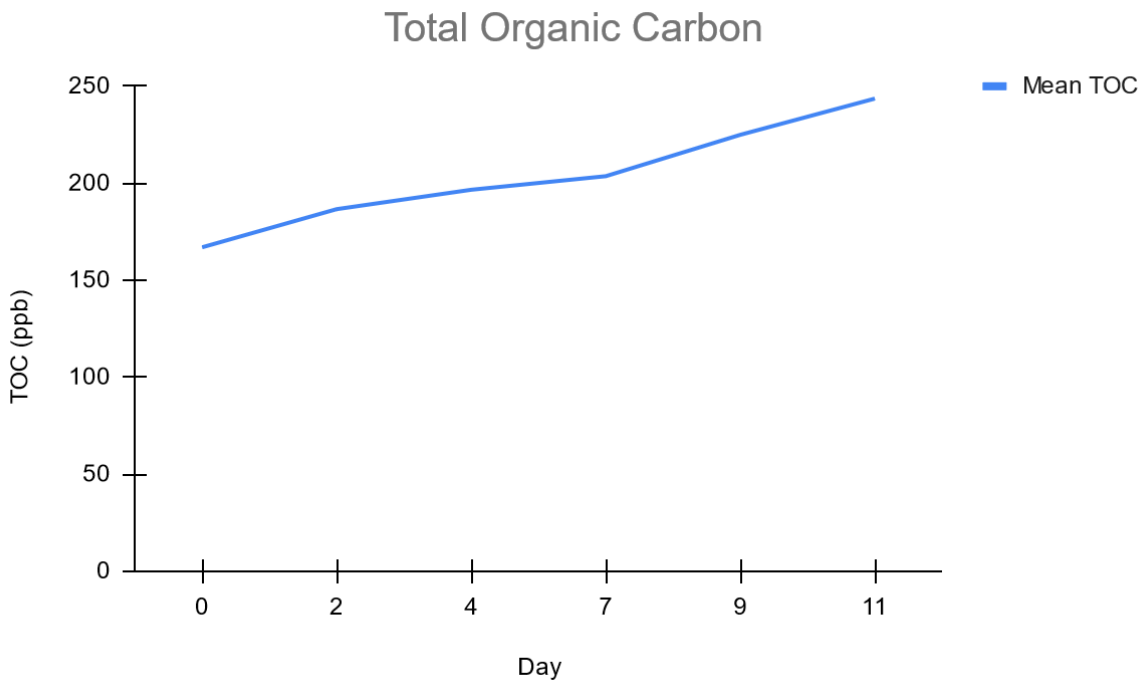

Figure 5. TOC

Compared to the results of other parameters, the TOC readings are observed to have an upwards trend (Figure 4). Despite that, the upwards trend of the TOC reading may indicate that the build up of contaminants that may result from bacterial contamination or from the environment. As a result, TOC build up may be a major factor in the limits of holding time in room temperature. A main cause of TOC in the water for injection may come from the use of alcohol by personnels to sterilize their gloves and instruments using the room. The laminar air flow used to prevent aerobic microbes from entering the containers during the sampling time does not prevent the alcohol vapors from contaminating the water for injection. This may be prevented by using a hosing and valve to reduce the contact with outside air when in use or during sampling, which may reduce the amount of TOC

TOC measurements are done to ensure the water for injection used does not contain organic carbon. Organic carbon in water for injection may be a sign of microbial contamination, due to the formation of biofilms that may affect the production facility. In addition, even if the TOC does not come from microbial sources, large amounts of alcohol in the water for injection may cause damage to the products when used as well due to changing the pH and other properties of the water for injection

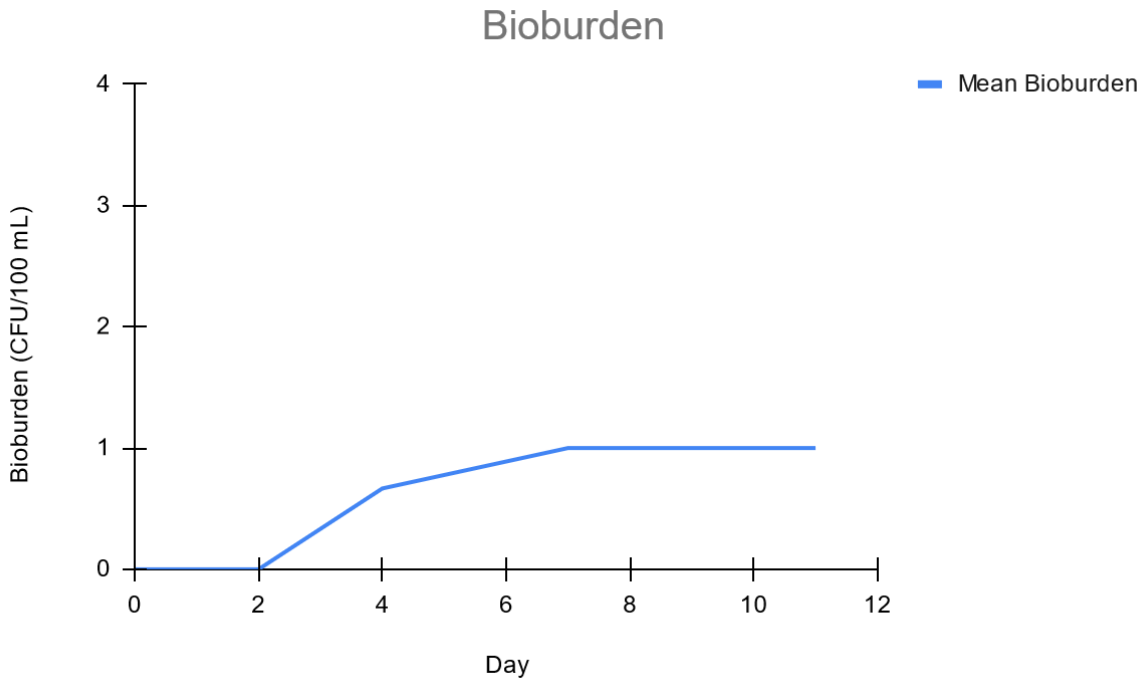

Figure 6. Bioburden

Based on the results, small amounts of microbes are able to enter, resulting from the original water for injection or through the sampling process. Bioburden refers to the amount of microbial presence in the water for injection (Figure 5). Microbial presence includes bacteria, yeast, and mold. Microbial growth is the greatest cause of contamination, capable of producing TOC and endotoxin in the water. Small colonies can easily grow quickly under room temperature and as such, may cause severe damage to the product if used in production. An example of a microbe that may grow in water for injection is *Burkholderia cepacia,* which may cause fever and shortness of breath to anyone contracting it. The results in Figure 5 shows that the bioburden is about 1 CFU/100 mL after storing more than 10 days. This value is less than 10 CFU/100 mL (Farmakope Indonesia standards). Then during this storage time, the quality meets the requirements.

Several factors prevent microbial growth from occurring in the container. The container is sealed after sterilization and fully filled with water, leaving very little aerobic microbes in the container to start a colony. Sterile gloves are used during the sampling to prevent contamination from personnels. Laminar air flow minimizes the growth of microbes during storage. Laminar air flow is capable of filtering up to 99% of the incoming air borne microbes (Thomas & Simmons, 2018).

In ultrapure water such as water for injection, microbes that live inside are often mold or gram negative bacteria. Mold is able to produce its own form of nutrients to survive a long period of time, however it is harder to enter the facilities as personnels changes into gowning before entering and the air inside is filtered, causing the chance of spores entering the facilities to be extremely low. Gram negative bacteria are able to enter the water for injection and its multi laminate structure made of many layers of phospholipid allows for the bacteria to survive the hypotonic environment. In order to survive for long periods of time, it will multiply and create biofilms to attach itself to the walls of the container. Once it receives some nutrients, such as if it is able to enter the culture, it will rapidly spread, increasing the bioburden load and spreading large amounts of endotoxin and TOC (Mittleman, 2019).

Table 3. Endotoxin Results

Run	Day	Acceptance Criteria	Endotoxin (Eu/mL)	Pass/Fail
1	0	<0.25 Eu/mL	<0.25	Pass
	2	<0.25 Eu/mL	<0.25	Pass
	4	<0.25 Eu/mL	<0.25	Pass
	7	<0.25 Eu/mL	<0.25	Pass
	9	<0.25 Eu/mL	<0.25	Pass
	11	<0.25 Eu/mL	<0.25	Pass
2	0	<0.25 Eu/mL	<0.25	Pass
	2	<0.25 Eu/mL	<0.25	Pass
	4	<0.25 Eu/mL	<0.25	Pass
	7	<0.25 Eu/mL	<0.25	Pass
	9	<0.25 Eu/mL	<0.25	Pass
	11	<0.25 Eu/mL	<0.25	Pass
3	0	<0.25 Eu/mL	<0.25	Pass
	2	<0.25 Eu/mL	<0.25	Pass
	4	<0.25 Eu/mL	<0.25	Pass
	7	<0.25 Eu/mL	<0.25	Pass
	9	<0.25 Eu/mL	<0.25	Pass
	11	<0.25 Eu/mL	<0.25	Pass

Based on the analysis of the endotoxin contents, the endotoxin level passed the acceptance criteria which was detected less than 0.25 Eu/mL based on the test, and as such endotoxin contents is considered too low to pose damage (Table 3). Endotoxins are dangerous compounds especially in the production of pharmaceutical products, as it may cause illness to the consumer. Endotoxin, also referred to as liposaccharides (LPS), is a molecule found in gram negative bacteria. Found in the outer cell membrane of the bacteria, a single cell may contain two million LPS molecules. LPS has three main components, lipid A, core oligosaccharide, and the O-specific chain representing the surface antigen (O-antigen). Endotoxin is dangerous when entering the bloodstream of humans, capable of resulting in fever, hypertension, adult respiratory distress syndrome, disseminated intracellular coagulation, up to endotoxin shock. Due to its ability to induce fever, endotoxin is often referred to as pyrogens. In addition, it is capable of causing sepsis as LPS can trigger the production

of inflammatory mediators such as cytokines IL-1b, IL-6 and TNF-a. A problem with endotoxin is that endotoxin does not break down in high temperatures up to 180 ℃, causing conventional means of sterilization not effective against endotoxin. Contaminated equipment required rigorous cleaning to be able to remove the endotoxin contents from it and as such, it is important that low endotoxin levels can be observed and maintained (Li & Boraschi, 2016).

III.3. Conclusion and recommendation

Based on the results, the measurements of the pH, conductivity, TOC, bioburden, Endotoxin, and appearance of the water sample does not exceed the acceptable criteria during the study period. Therefore, water for injection can be stored safely in room temperature for two weeks under laminar air flow.

Future works can be done to compare different methods of storing and taking water for injection containers to prevent build up of different contaminants such as TOC and bioburden. Using valve pipes can reduce the amount of contact with the air when sampling or using the water. A longer amount of time frame for each run can improve the results as well for future projects.

IV. SELF REFLECTION

During the internship, I have learned multiple things across my time here. An important skill I have learned is aseptic techniques in production facilities. In the production facilities, aseptic techniques used to keep materials clean and sterile is more rigorous compared to the requirements in the campus labs, due to the bigger consequence for each contamination. The techniques include gowning, material transfers, use of laminar air flow, and cleaning different equipment and apparatus. Through this experience I have become more familiar with the industry. Through the project, I have learned more about drafting and designing a proposal and project. I was given the opportunity to draft the proposal and observe the approval process. Through the experience, I have improved my drafting skills. During the internship, I have learned about my strengths and weaknesses. My weakness is that I have a difficulty in focusing and tend to get distracted. However, I have learned that my strengths include my patience and my creativity. I3L has prepared me with the knowledge I need to function and its values have helped me in establishing a strong morale. Out of the many lessons I have learned in I3L, the subjects I have used most are cell tissue culture classes, which familiarized me with the cell cultures of production. Another course I used the skills from is scientific writing, which guided me through the proposal process. The bright sessions have helped me in my work during the proposal process. My project serves to assist the production of the various products in KGM. Through the Hold time study, flexibility of maintenance of the water filtration system is increased, ensuring that there is less need to interrupt production for maintenance. Thus, increasing the productivity of the plant.

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V. CONCLUSION & RECOMMENDATION

Overall, I believe that I have successfully completed my goals as well as the necessary requirements for this internship. I have worked in KGM for four months and participated in project work. Overall, the internship helped me learn about real work and the industry procedure and has been beneficial for my future. Perhaps a clearer guidance can be assigned to the intern to increase the effectiveness of the internship as I am often left confused about my daily duties.

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APPENDICES

Table A1. Conductivity requirements based on temperature for stage 1 and stage 2 conductivity testing, take from United States of America's pharmacopeia (USP)

Temperature	Conductivity Requirement (µS/cm)
0	0.6
5	0.8
10	0.9
15	1.0
20	1.1
25	1.3
30	1.4
35	1.5
40	1.7
45	1.8
50	1.9
55	2.1
60	2.2
65	2.4
70	2.5
75	2.7
80	2.7
85	2.7
90	2.7
95	2.9
100	3.1

Table A2. Conductivity requirements based on pH for stage 3 conductivity testing taken from USP

pH	Conductivity Requirement (µS/cm)
5.0	4.7
5.1	4.1
5.2	3.6
5.3	3.3
5.4	3.0
5.5	2.8
5.6	2.6
5.7	2.5
5.8	2.4
5.9	2.4
6.0	2.4
6.1	2.4
6.2	2.5
6.3	2.4
6.4	2.3
6.5	2.2
6.6	2.1
6.7	2.6
6.8	3.1
6.9	3.8
7.0	4.6

Table A3. Conductivity requirements based on temperature for stage 1 and stage 2 conductivity testing, taken from Farmakope Indonesia

Suhu	Persyaratan Konduktivitas (µS/cm)
0	0,6
5	0,8
10	0,9
15	1,0
20	1,1
25	1,3
30	1,4
35	1,5
40	1,7
45	1,8
50	1,9
55	2,1
60	2,2
65	2,4
70	2,5
75	2,7
80	2,7
85	2,7
90	2,7
95	2,9
100	3,1

Table A4. Conductivity requirements based on pH for stage 3 conductivity testing taken from Farmakope Indonesia

pH	Persyaratan Konduktivitas (µS/cm)
5,0	4,7
5,1	4,1
5,2	3,6
5,3	3,3
5,4	3,0
5,5	2,8
5,6	2,6
5,7	2,5
5,8	2,4
5,9	2,4
6,0	2,4
6,1	2,4
6,2	2,5
6,3	2,4
6,4	2,3
6,5	2,2
6,6	2,1
6,7	2,6
6,8	3,1
6,9	3,8
7,0	4,6