Historical and hygienic aspects on roles of quality requirements for antibiotic products in Japan: Part 5 - Introduction of technology and knowledge on streptomycin production from the United States of America

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In order to investigate the roles of quality requirements for antibiotics products in Japan, from historical and hygienic aspects, we examined how technology and knowledge in the production and quality control of streptomycin were introduced from the United States of America.

In this study, through detailed investigations and analyses, it was confirmed that the introduction of technology and knowledge on streptomycin was strongly supported by Brigadier General Crawford Sams, the chief of the Public Health and Welfare Section (PHW) of the Supreme Commander for Allied Powers/General Headquarters, via the Ministry of Welfare in Japan.

Dr. Selman Waksman, the discoverer of streptomycin, along with scientists of Merck & Co., also helped Japanese industries extensively, via PHW, by providing the original streptomycin-producing strains and transferring expertise in streptomycin production.

With the technology and knowledge being introduced from the USA, domestic production of streptomycin preparations increased very rapidly. As noted in our previous report, domestic production reached amounts enough to satisfy national demand within three years. Japanese people have a racial tendency to be highly susceptible to tuberculosis known as an incurable national disease. Thanks to streptomycin therapy, the tuberculosis mortality rate (per 100,000 population) had fallen dramatically within only five years from 187.2 in 1947 to 82.2 in 1952.

\textsuperscript{1) Dedicated to pioneers in antibiotic research of Japan on the occasion of the 70\textsuperscript{th} anniversary of Japan Antibiotics Research Association established on the 26\textsuperscript{th} August of 1946.
Introduction

Industrial production of penicillin in Japan reached an amount sufficient enough to fill domestic demand within a three-year period, as described in our preceding report\(^1\), under the strong support of Colonel Crawford F. Sams, the chief of the Public Health and Welfare Section (PHW) of the General Headquarters, along with the Supreme Commander for the Allied Powers (GHQ/SCAP), who established the plan\(^2\) for improving the healthcare system in a devastated post-wartorn country.

Penicillin contributed greatly to the health maintenance of the Japanese people by showing remarkable effects against life-threatening infectious diseases such as septicemia, endocarditis, pneumonia, meningitis, and tetanus. However, it was ineffective against tuberculosis which was the number one cause of death in Japan around 1947, with a mortality rate\(^3\) of 187.2 per 100,000 of the population. Tuberculosis was known as an incurable Japanese national disease and bed rest therapy was the sole treatment for the disease prior to 1950.

For the PHW, gaining control of tuberculosis was an important issue for reasons related to carrying out the occupation policies of the GHQ/SCAP, as well as maintaining the health of the stationed soldiers. Measures were also undertaken to consolidate the national sanatoriums and prevent the spread of TB by use of BCG inoculations. The PHW decided to promote domestic streptomycin production for the purpose of tuberculosis suppression, especially in light of the high evaluation of the prior achievement of domestic penicillin production in Japan within a short period of time. The detailed involvement of the PHW in the establishment and promotion of the penicillin industry in Japan was verified and described\(^1\) in Part 3 of our preceding report.

In this report we shall discuss the background and process of the introduction of the technology and knowledge in streptomycin production from the United States of America (USA), under the extensive support of the PHW.

I. Methods of Investigation

The general method for resource acquisition was described in detail in the first report\(^4\) of our investigation.

The original results of Japan’s own research in streptomycin production and the details of the import of streptomycin preparations from the USA were obtained from the daily records of the Japan Penicillin Research Association (JPRA), published periodically in the Journal of Antibiotics.

The details of the transfer of information on streptomycin research in the USA were obtained from the Weekly Bulletin\(^5\) of the PHW, with the permission of Professor Sugita of Oita University who reproduced the documents.
The acquisition of documents on the achievement of domestic production of streptomycin was described in Part 2 of our preceding report.

II. Results

In the course of exploratory research on novel antibiotics produced by soil actinomycetales, Dr. SELMAN A. WAKSMAN and his research group at Rutgers University discovered streptomycin possessing activity against the tubercle bacillus in the culture broth of a strain of *Streptomyces griseus* in 1944. The therapeutic effect of streptomycin on human tuberculosis was confirmed by Dr. H. CORWIN HINSHAW and his group at Mayo Clinic in 1946.

Dr. JACKSON W. FOSTER, a student of Dr. WAKSMAN’s, was well-informed about the discovery of, and the clinical trials with, streptomycin prior to his arrival in Japan as a consultant on penicillin production. When Dr. FOSTER received a report that the penicillin plant at Merck & Co., constructed by him during wartime, was also being applied toward streptomycin production, he gave a lot of information pertaining to streptomycin research to Dr. HAMAO UMEZAWA, of the Research Institute for Infectious Diseases (RIID) of Tokyo Imperial University. At the farewell party for Dr. FOSTER, held in March of 1947 for the occasion of his return to the USA, he informed Japanese scientists about the necessity to begin preparations for the domestic production of streptomycin.

1. Attempts to produce streptomycin by Japan’s own technology

The Division of Antibacterial Substances (DAS) was established in the newly organized National Institute of Preventive Medicine and Hygiene (NIPMH) in May of 1947 and Dr. UMEZAWA was appointed the director of the division. Exploratory research on new antibiotics produced by soil actinomycetes was conducted at the division and isolation of a streptomycin-like substance was reported at the 10th Research Meeting of JPRA held on the 18th of July 1947. The substance was later confirmed to be streptomycin and the producing strain was identified to be *S. lavendulae*, which was different at the species level from WAKSMAN’s strain (*S. griseus*). From the division, some novel methods for the rapid identification of streptomycin-producing microorganisms were also reported.

Toward the domestic production, exploratory research to isolate streptomycin-producing strains was conducted for about two years at several laboratories in universities and pharmaceutical industries. Although some results were reported, no suitable strain for industrial production was able to be obtained. In those days, the patent system applicable for microbial products obtained by fermentation was a so-called “process patent” and different from today’s “substance patents.” Under the “process patent,” one may commercially produce a particular microbial product from a strain belonging to a different species of the same genus described in prior patents without
confliction. Under such circumstances, active research to obtain different strains, other than Waksman’s *S. griseus*, was conducted\(^\text{16,17}\) with the aim of producing streptomycin domestically.

The PHW evaluated highly the development of domestic penicillin production, which had attained a monthly output of 50 billion units within two years of the introduction\(^\text{1}\) of US technology through the lectures of Dr. Foster. The manufacturing of crystalline penicillin G\(^\text{18}\) with a purity of 90% or above was also noteworthy. Therefore, the PHW created a plan to promote the domestic production of streptomycin as the second antibiotic drug in Japan.

Taking the intention of the PHW into consideration, the Pharmaceutical Affairs Bureau (PAB) of the Ministry of Health and Welfare (MHW) convened experts in penicillin production, from approximately 10 pharmaceutical companies. On the 16\(^{th}\) of September 1948, they discussed\(^\text{19}\) the logistics for streptomycin research and conditions necessary in order to begin streptomycin manufacturing at an industrial scale at each company. Thereafter, the Preventive Medicine Bureau (PMB) of the MHW convened\(^\text{20}\) a board of scientists and physicians, under the attendance of the chief of the Bureau and directors of related Divisions, to discuss how to initiate measures on streptomycin research. The participants involved were as follows: Drs. Rokusō Kobayashi, Hamao Umezawa and Ken Yanagisawa of NIPMH, Teijirō Yabuta and Yusuke Sumiki of the Department of Agricultural Chemistry (DAC), Faculty of Agriculture (FA), the University of Tokyo (UT), Morizo Ishidate of the Pharmaceutical Institute, Medical Faculty of the UT, Hajime Tamura of the Department of Urology, Keio University School of Medicine, Hidejiro Haruki of the National Nakano Sanatorium, and Yukimasa Yagisawa of the JPRA.

Pilot production of streptomycin had been conducted, with the lead taken by NIPMH, and a request\(^\text{21}\) given to the JPRA from the Ministry of Education, Science and Culture (MESC) to divide some portions of the Grant-in-aid for Scientific Research (GASR) provided, in the amount of ¥3 million for the fiscal year of 1948, and apply it towards streptomycin research. The prospect on the progress of streptomycin research was described\(^\text{22}\) in an application form to the GASR of the MESC for the fiscal year of 1949. It noted that pilot production should be accomplished within one year’s time, with an additional year necessary until the supply for commercial products by industrial processes could be reached.

While the pilot production of streptomycin at the DAS of the NIPMH progressed smoothly, some difficulties did occur during the production by submerged culture, utilizing steel tanks for penicillin production, affecting the potency. Potency by submerged culture reached as low as 150 units/mL, but eventually 300 - 800 units/mL was attained via the shake-culture in glass flasks. After several repeated failures, the reason for the low productivity was elucidated\(^\text{23}\). Ferrous ions, dissolved from the penicillin tank made of steel, interrupted streptomycin formation. It was later confirmed that either rubber coating or tinning of the steel tanks, or the use of stainless steel tanks, were effective\(^\text{10}\) remedies to eventually attaining higher production potencies.
2. Import of streptomycin preparations and establishment of the Research Council on Streptomycin

While verifying the effects of streptomycin via the results of the clinical trials among 3,032 tuberculosis patients in 48 hospitals, conducted for two years since June 1946 by the US Veterans Administration, the PHW distributed streptomycin preparations. The distributions were included in the relief supplies of the “Licensed Agencies for Relief in Asia; LARA (started from March 1946)” to specified hospitals throughout Japan. The clinical results of the distributed streptomycin preparations were reported at meetings of the JPRA expert committee held in June and September of 1948, under the titles of “Clinical cases treated with the streptomycin of the Gift-packages.”

It was described in the PHW Weekly Bulletin, for the period of early January 1949, that commercial streptomycin production was expected to reach a volume adequate to satisfy the minimum needs in Japan by the end of that year. Furthermore, in order to supply enough streptomycin until domestic preparation became available, the PHW inquired with the US Government about the possibility of importing sufficient amounts of streptomycin preparations for the treatment of Japanese tuberculosis cases. The request was approved by the US Government and the first shipment was scheduled to arrive in Japan within one month to six weeks. The PHW also described, by means of devoting large spaces of the bulletin publication, summaries of the above-mentioned clinical trials conducted by the US Veterans Administration, along with information on the usefulness of chest X-rays, characteristics of tuberculosis in various organs, and the adverse effects of streptomycin.

The anticipation of the Japanese people for the efficacy of streptomycin was very great. At the Committee on Health and Welfare of the House of the Councillors of the 5th Session of the Diet, held on the 17th of March 1949, Mr. Katsuma Kobayashi, a member of the House belonging to the Democratic Party of Japan, submitted a memorandum of questions under the title of “regarding streptomycin - the wonder drug for tuberculosis.” It inquired about (1) reports on experiments or clinical cases concerning streptomycin efficacy, (2) records of the distribution of imported streptomycin, (3) the situation of domestic streptomycin production, i.e. names of factories, their abilities and expected time frames for marketing, and (4) future intentions for the promotion of streptomycin production. Interestingly, the written answer was sent under the name of Mr. Shigeru Yoshida, the Prime Minister, and not under the name of Mr. Takeo Kurokawa, the Minister of the MHW. In response to the second question, it was mentioned that streptomycin preparations in the amount of 200 kg (for 5,000 patients), slotted for import at the end of March, would be distributed in accordance with advice given by the Research Council on Streptomycin (RCS) to national hospitals, national sanatoria, medical institutions, and general hospitals. Beside such clinical uses, some portions for fundamental research would also be distributed to research institutes, including the DAS of the NIPMH, universities, national hospitals,
and national sanatoria.

In reality, 209 kg streptomycin preparations were first imported at the end of March 1949. It was equivalent to 5,225 cases to be treated, since the total dose for one patient was 40 grams. The price was set as low as $1.30 (¥351.-) per gram and the total cost of the import came to $271,700, equivalent to ¥73,359,000.- (at the exchange rate of $1 = ¥270.-). At that time the Japanese government did not have enough “foreign exchange allocation,” therefore payment was settled by the Government Appropriation for Relief in Occupied Area (GARIOA) fund under the discretion of GHQ/SCAP.

The MHW established the RCS for the purposes of the appropriate distribution of imported streptomycin and the promotion of both fundamental and industrial research on streptomycin production.

A notice, jointly signed by chiefs of the PMB and the PAB of the MHW, was issued to prefectural Governors describing the background of the imports and the purposes for the distribution of streptomycin. Also included were instructions for the methods of patient selection, regimen creation, and the evaluation of clinical effects. In the notice, exceptionally deep gratitude was expressed to GHQ/SCAP for the courtesies of setting the price extremely low and allotting the GARIOA fund expressly for the purchase of streptomycin preparations. These chiefs were responsible, at that time, for the control of tuberculosis, which was the leading cause of death nationally. Records showed the number of newly afflicted patients at 465,000 (morbidity rate of 565.7 per 100,000 population) and the number of deaths at 138,000 (mortality rate of 168.8 per 100,000) in 1949. Import of the “wonder drug - streptomycin” was very helpful in carrying out their disease control duties.

At the inauguration ceremony of the RCS, held at the auditorium of the RIID of the UT on the 21st of June 1949, in the presence of the Minister of the MHW, Brigadier General SAMS (promoted in April 1948) delivered a speech. The speech revealed that the necessary amount of streptomycin in Japan was 15,000 kg per year and that the total amount of imported streptomycin was 600 kg. Since this was only 1/25 of the demand, an increase in efforts to archive domestic commercial production was necessary.

The clinical trials of the first imported streptomycin was conducted by 31 members of the RCS at 20 hospitals/sanatoria during May - October 1949 and the results of 679 cases were as follows: effective 474 [69.9%; cure 71 (10.5%) and remission 403 (59.4%)], persistence 139 (20.4%), deterioration 14 (2.1%), and deaths 52 (7.6%). It should be noted that the preparation used for the trials was streptomycin trihydrochloride-calcium chloride double salt made by Merck & Co. and the package insert for the preparations was translated into Japanese and distributed to the hospitals/sanatoria involved in the trials.

A total amount of 400 kg streptomycin (equivalent to an amount adequate for 10,000 patients) arrived on the 7th of October 1949, as the second import. The exchange rate was revised to
be fixed at $1^{50} = ¥360.- starting from the 1st of April 1949 and the price of streptomycin for the second import was $1^{24} (¥700.-) per gram. Therefore, the sum came to ¥280 million, which was equivalent to 0.04% of the general account budget of Japan (¥699.4 billion) for the fiscal year of 1949.

The imported streptomycin preparations were stored at the warehouses of 12 pharmaceutical companies\(^3\) responsible for distribution (100 kg at Takeda Chemicals, 50 kg at Shionogi, 30 kg each at Tanabe Pharmaceutical, Fujisawa Pharmaceutical, Yamanouchi Pharmaceutical, Dainippon Pharmaceutical, and Daiichi Pharmaceutical, and 20 kg each at Sankyo, Torii Pharmaceutical, Tokyo Tanabe, Banyu Pharmaceutical, and Nakamura-Taki Pharmaceutical). These streptomycin preparations were scheduled to be distributed to 9,200 patients throughout Japan (e.g., Tokyo 911, Osaka 490, Fukuoka 469, Kanagawa 390, Aichi 370, Chiba 322, and Kyoto 315 patients). Facilities (national sanatoria, national hospitals, and university hospitals) to accommodate these patients, along with the number of patients for each prefecture and specific facility sites depending on the number of available tuberculosis therapy experts, were designated by a notice\(^3\) issued by the chief of the PAB of the MHW.

3. Initiation of streptomycin production with the support of the PHW

The plan listed for 1949, by the PHW, to produce streptomycin on an industrial scale was approved by GHQ/SCAP and the MHW recognized the usefulness of streptomycin for tuberculosis treatment. A target was set to produce streptomycin domestically in sufficient amounts to fill minimum demands by the end of 1949.

However, it was described\(^15\) in the PHW Weekly Bulletin that there existed no appropriate strain for the use of commercial streptomycin production, despite extensive research on streptomycin having been conducted for approximately two years at several laboratories in Japan. Under such circumstances, the PHW obtained two *S. griseus* strains for producing streptomycin from Dr. Waksman and passed them on to the NIPMH on the 28th of December 1948. It was also mentioned that the provided strains were patent protected property of the Rutgers Research and Endowment Foundation (RREF), being used throughout the world for the commercial production of streptomycin. Therefore, a license agreement would be necessary between any company involved and the RREF, when commercial production commenced under the supervision of the NIPMH.

In the same PHW Weekly Bulletin, it was mentioned\(^15\) that the supply of these strains was in response to a request by the Japanese Government to GHQ/SCAP and not at the suggestion of the PHW. Such an approach by the PHW, to state independent status from the Japanese Government, was consistent with the expectations of the initial invitations of Dr. Foster for penicillin production and suggests the basic idea of the occupation policy of GHQ/SCAP.

In the early stages in Japan, research on the production and clinical applications of streptomycin was promoted by the GASR of the MESC and remarkable accomplishments were ob-
tained. In the fiscal year of 1949, ¥6.2 million, out of a total of ¥7.0 million allotted to antibiotic research\(^\text{37}\), was divided up for different categories of streptomycin research: ¥4.5 million for production, including ¥2.0 million for running costs of the pilot plant, ¥1.5 million for clinical investigations, and ¥0.2 million for administrative purposes.

At the first meeting\(^\text{30}\) of the Production Division of the RCS (PD-RCS), scheduling perspectives were sought for the start of tank-fermentation and prospective yields for domestic commercial production by March of 1950. Research subjects were categorized into 1) collection of strains, 2) cultivation, 3) purification, 4) facilities for culture and purification, and 5) assay. A notable discussion took place at this meeting regarding the US strains \textit{S. griseus} 18-16 (strain No. R\(_4\)-3463) and its progeny strain No. R\(_4\)-3475, both of which originated from Waksman’s laboratory\(^\text{10,38}\). The maximum amount of streptomycin production was as low as 100-200 units/mL. Subsequently, the PD-RCS requested that the PHW, through the MHW, provide better quality strains enabling higher streptomycin productivity. The request made with GHQ/SCAP and the research institutes in the USA (i.e., Waksman’s laboratory at Rutgers University and the research laboratory of Merck & Co.), recognized that the Japanese research group already possessed\(^\text{13, 23}\) the necessary techniques and requisite knowledge to produce streptomycin on a large scale.

At the second meeting\(^\text{39}\) of the PD-RCS, held on the 22\(^{\text{nd}}\) of July 1949, the DAS of the NIPMH requested that 40 g of the imported streptomycin be provided monthly in order to establish a national certification procedure and the “Minimum Requirement of Streptomycin.” The latter was under preparation by referring to the provisions on streptomycin drugs described in the Code of Federal Regulations Title 21, issued by the U.S. Food and Drug Administration (FDA).

It was also decided, at the same meeting, to provide a considerable part of the experimentally produced streptomycin to Dr. Morizo Ishidate for his research on the synthesis of streptomycin derivatives. The initiation of the derivative synthesis at such an early stage might be due in part to the tradition of the “creation of novel drugs” in Japanese pharmaceutical sciences (since the time of Dr. Nagayoshi Nagai\(^\text{40}\), the first president of the Pharmaceutical Society of Japan) and by a desire to avoid already known adverse reactions to streptomycin.

At the third meeting\(^\text{41}\) held on the 17\(^{\text{th}}\) of September 1949, it was decided among the seven laboratories in charge of the improvement of the strains and culture methods, to compare the two strains from Waksman’s laboratory and the thirteen strains isolated domestically by use of the culture media invented by Dr. Waksman and the media created at the individual laboratories. As an interim report on the isolation of the producing strains from over 1,000 soil isolates, one strain was found to produce 300 units/mL or more streptomycin by a shaking culture method. A successful strain improvement was also reported on the Waksman strains by the UV-right irradiation and mono-spore isolation techniques. Regarding purification, it was reported that the application of ion-exchange resin was promising. Additionally, a chemical conversion of streptomycin into dihydrostreptomycin by a novel catalytic reduction under normal pressure was reported.
At the fourth meeting\(^{42}\) held on the 16\(^{th}\) of December 1949, the results comparing the 15 strains distributed at the previous meeting were reported to have attained a production of 500 - 1,100 units/mL streptomycin, but became unstable upon reaching 1,200 units/mL or above. Furthermore, some of the newly isolated strains from the soil were found to produce 460 - 900 units/mL streptomycin. Such results were comparable to those published during the period from 1947 to 1949 by the US Pharmaceutical companies (i.e., Drs. Alfred R. Stanley\(^{43}\) of Commercial Solvent, George M. Savage\(^{44}\) of Upjohn, and Max Tishler\(^{45}\) of Merck & Co.). It could be said that the bleeding technology for antibiotic producers in Japan had already reached a comparable level to that of the USA at the time. On the other hand, in the experimental production at the pilot plant, strain Y-41 yielded 300 units/mL streptomycin in submerged culture using a stainless or tinning tank.

At the sixth meeting of the PD-RCS\(^{46}\) held on the 26\(^{th}\) of June 1950, the production yields were reported to be approximately 990 units/mL by shaken culture in flasks and constantly around 500 units/mL by submerged culture in tanks. Regarding purification, while the crude powder obtained by the charcoal absorption method possessed a potency of 180-280 units/mg, those obtained by the method of combination of charcoal absorption and solvent extraction possessed 340-490 units/mg. Those obtained solely by the method of solvent extraction possessed 460-530 units/mg; those by the ion-exchange method possessed 538-819 units/mg. In particular, in the ion-exchange method, the carboxylic cation exchange resin developed by Mitsui Chemical showed remarkable efficacy when compared to the usual sulfonic cation exchange resin in the purification of streptomycin.

**4. Governmental purchasing of the domestically produced streptomycin**

Having a strong conviction that the manufacturing technology of streptomycin had been adequately established and that domestic commercial production was close at hand, the 3\(^{rd}\) Yoshida Cabinet decided\(^{47}\), on the 22\(^{nd}\) of September 1949, that 1) it was necessary to establish a way for the domestic production of streptomycin to proceed in order to secure a stable supply, 2) in taking measures in preparation for domestic production, advanced technology and appropriate facilities would be introduced from the USA with the Government supporting costs and material procurements, and 3) the budget to purchase domestically produced streptomycin be duly appropriated.

Responding to the cabinet decision, the MHW took budgetary steps to purchase the domestically produced streptomycin. Meanwhile, several companies belonging to the PD-RCS conducted pilot production of streptomycin by tank fermenters and submitted applications for the approval of commercial production to the MHW. In April of 1950, the MHW gave approval to five companies, Meiji Seika, Kyowa Fermentation, Kaken, Nikken Chemical, and Shimane Chemical, for the commercial manufacture of streptomycin and eagerly encouraged domestic production.

Meiji Seika began fundamental studies on streptomycin\(^{48}\) in September of 1947, initiated
test production by pilot tanks in July of 1948, requested the formulation of governmental policy to promote domestic production at a hearing by the MHW held in September of that same year, and played important roles in the PD-RCS since its establishment in September of 1949. At this company, two sets of 46-ton tanks for the production of streptomycin were operated in 1950.

Kyowa Fermentation had substantial experience in penicillin production by use of Japan’s largest tank, 4 tons in size, since September of 1947; attainment of a monthly penicillin manufacture of 1,000 vials of 30,000-unit preparations was reached in April and 14,000 vials of 100,000-unit preparations in December of 1948. This company began fundamental studies on streptomycin in September of 1948 and aimed to initiate commercial production by three 2-ton tanks with a producing strain supplied from Dr. TOSHINOBU ASAI of the DAC-FA-UT. In 1950, three 8-ton tanks began operations producing streptomycin (reported by Dr. SHUKURO KINOSHITA, in personal communications).

Kaken initiated their fundamental studies on streptomycin in April of 1948, began test production by a 200-liter tank in November of the same year, and sent leading scientists of that time (Drs. TEIJIRO YABUTA, KINICHIRO SAKAGUCHI, and YOSHITOSHI OYAMA) to the PD-RCS as core committee members. Independent from the RCS plan to establish a pilot plant, Kaken built its own pilot plant equipped with three 600-liter tanks and started their operation in October of 1949. This initiative took place under the presidential leadership of Dr. YOSHIO NISHINA. Commercial production using these tanks started on the 1st of May 1950. During the first-half of 1950, the total production of streptomycin was only 200 g, but when operation of the three 6-ton tanks was started in October 1950, the total production for the second-half of the year reached 71.4 kg. Three 60-ton tanks were constructed and began operation on the 27th of September 1951; maximum production of these tanks was recorded to have reached 2,300 units/mL using the producing strain Ku-M11-106 (as reported by Dr. SHIGEO FUJITA, in personal communications).

The ceremony for the first governmental purchasing of domestically produced streptomycin was held on the 18th of July 1950, in the Minister’s room at the MHW. In attendance were the Minister, chiefs and directors of the responsible Bureaus and Divisions of the MHW, Brigadier General SAMS and Dr. BAND of the PHW, and representatives of the five companies who produced the streptomycin. A total of 1,160 vials containing 1.0 g (potency) of streptomycin trihydrochloride were purchased; 1,000 vials produced by Meiji Seika and 40 vials each by Kyowa Fermentation, Nikken Chemical, Kaken, and Shimane Chemical.

An outline of the purchasing process was noted by the PAB of the MHW, on the 6th of October 1950. It was indicated by the buying plan as outlined in Table 1A. The actual results of the domestic production and purchase, by the end of September of 1950, were also noted (Table 1B). In addition, the plan to import streptomycin preparations for three quarters, from July 1950 to March 1951, was referenced (Table 1C). The reported ratios of the amounts of domestic production (Table 1A) to that of the imported preparations (Table 1C) were at 1/80 (Quarter 1) - 1/9
As reference information, the transition of streptomycin production in these five companies during the second-half of 1950, along with the size of the equipped tanks, was also published (Table 2).

### Table 1. Outline of the purchasing of domestically produced streptomycin

<table>
<thead>
<tr>
<th>Period</th>
<th>Purchase amount (potency)</th>
<th>Procurement unit price</th>
<th>Total budget</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quarter 1: Jul - Sep 1950</td>
<td>20 kg</td>
<td>¥1,300/g</td>
<td>¥26,000,000</td>
</tr>
<tr>
<td>Quarter 2: Oct - Dec 1950</td>
<td>70 kg</td>
<td>¥1,100/g</td>
<td>¥77,000,000</td>
</tr>
<tr>
<td>Quarter 3: Jan - Mar 1951</td>
<td>186 kg</td>
<td>¥900/g</td>
<td>¥167,400,000</td>
</tr>
<tr>
<td>Quarter 4: Apr - Jun 1951</td>
<td>588 kg</td>
<td>¥600/g</td>
<td>¥353,340,000</td>
</tr>
<tr>
<td>Total</td>
<td>864 kg</td>
<td>¥721/g (avg.)</td>
<td>¥623,740,000</td>
</tr>
</tbody>
</table>

B. Results of production and purchase (by the 30th of September 1950).

<table>
<thead>
<tr>
<th>Company</th>
<th>Production (potency)</th>
<th>Purchase (potency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meiji Seika</td>
<td>12,160 g</td>
<td>12,160 g</td>
</tr>
<tr>
<td>Nikken Chemical</td>
<td>5,240 g</td>
<td>5,185 g</td>
</tr>
<tr>
<td>Kyowa Fermentation</td>
<td>2,160 g</td>
<td>2,160 g</td>
</tr>
<tr>
<td>Shimane Chemical</td>
<td>295 g</td>
<td>295 g</td>
</tr>
<tr>
<td>Kaken</td>
<td>200 g</td>
<td>200 g</td>
</tr>
<tr>
<td>Total</td>
<td>20,055 g</td>
<td>20,000 g</td>
</tr>
</tbody>
</table>

C. The plan for import of streptomycin preparations.

<table>
<thead>
<tr>
<th>Period</th>
<th>Import amount (potency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quarter 1: Jul - Sep 1950</td>
<td>1,600 kg</td>
</tr>
<tr>
<td>Quarter 2: Oct - Dec 1950</td>
<td>1,400 kg</td>
</tr>
<tr>
<td>Quarter 3: Jan - Mar 1951</td>
<td>1,700 kg</td>
</tr>
<tr>
<td>Total</td>
<td>4,700 kg</td>
</tr>
</tbody>
</table>

(Quarter 3). As reference information, the transition of streptomycin production in these five companies during the second-half of 1950, along with the size of the equipped tanks, was also published (Table 2).

5. The introduction of US technology under contracts

The PHW convened a conference on streptomycin, on the 10th of March 1950. Responsible officers of the MHW and representatives of the RCS and pharmaceutical companies were in attendance. Brigadier General SAMS explained, in detail, the results of the search for and negotia-
tions on the introduction of technology for streptomycin production from the USA to Japan. In the USA, six companies were manufacturing streptomycin under individual patents and there were three ways to introduce the technology: (1) purchase and subdivide the bulk, (2) purchase inexpensive crude material and purify it, or (3) enter into a special contract with a US company, under the supervision of GHQ/SCAP, to transfer the expertise on streptomycin production. For the third option, it was thought to be possible to invite a technical expert from a US company as an advisor to the PHW and, depending on the results of site visits by the expert, make a special contract with the company.

Another conference on streptomycin, organized by the MHW, was held on the 14th of March 1950. In attendance, were the Administrative Vice-Minister and chiefs of the responsible Bureaus of the MHW, Drs. Band, Payne, and Bozeman of the PHW, Drs. Sumiki, Umezawa and Yagisawa of the RCS, and representatives of various pharmaceutical companies (Meiji Seika, Kyowa Fermentation, Kaken, Nikken Chemical, Takeda Chemicals, and Shionogi). Mr. Euler, the Vice-President of Merck & Co., received a special invitation in order to share the current state of streptomycin manufacturing in the USA and to take questions pertaining to the subject area of special contracts. Merck & Co. had several advantages in streptomycin production. Among them: patented expertise on the crystallization of streptomycin trihydrochloride-calcium chloride double salt (SM-HCl-CaCl₂), removal of histamine-like depressants with phenol, purification of streptomycin by carboxylic cation exchange resin (Amberlite IRC-50), and synthesis of dihydrostreptomycin by reduction with platinum catalysts.

The MHW, the RCS, and representatives from various pharmaceutical companies reached a

<table>
<thead>
<tr>
<th>Company</th>
<th>Equipped tank size*</th>
<th>Streptomycin production [ g (potency) ]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Jul</td>
<td>Aug</td>
</tr>
<tr>
<td>Meiji Seika</td>
<td>46 ton X 2</td>
<td>1,500</td>
</tr>
<tr>
<td>Nikken Chemical</td>
<td>4 ton X 6</td>
<td>330</td>
</tr>
<tr>
<td>Kyowa Fermentation</td>
<td>8 ton X 3</td>
<td>2,160</td>
</tr>
<tr>
<td>Shimane Chemical</td>
<td>2 ton X 3</td>
<td>295</td>
</tr>
<tr>
<td>Kaken</td>
<td>6 ton X 3</td>
<td>200</td>
</tr>
<tr>
<td>Total</td>
<td>1,700</td>
<td>2,390</td>
</tr>
</tbody>
</table>

* Data quoted from Yakugyo-Jiho (Pharmaceutical Times), 17th of January 1951.
consensus on how to introduce the know-how on streptomycin production from a US company under special contract and Merck & Co. was selected to be the candidate partner. Responding to the request of the PHW, Dr. ADDINALL (Foreign Scientific Manager) and Dr. COLIN, (director of Pilot Plant Division) of Merck & Co. came to Japan on the 3rd of May 1950. They visited and inspected prospective counterparty factories and other related companies through the 23rd of May. Related companies included Mitsui Chemical, Kaken, Meiji Seika, Mitsubishi Kako Instrument, Nikken Chemical, Takeda Chemicals, Tokunaga Glass, Shionogi and Kyowa Fermentation (in the order of visitation).

The second conference on streptomycin convened by the PHW was held on the same day as the 6th meeting of the PD-RCS. Brigadier General SAMS elaborated on the opinions of Drs. ADDINALL and COLIN, stating that they were very much impressed by the progress of the Japanese companies. It was specified that Merck & Co. would be able to make a contract with only one or two companies, not with all companies, because of prohibitions under antitrust laws. Brigadier General SAMS also mentioned that all companies were encouraged to make their own efforts to produce streptomycin commercially by a process other than the patented method of Merck & Company.

The reason why it was necessary to make a special contract with Merck & Co. and introduce their patented process, was that the domestically produced streptomycin trihydrochloride manifested many problems in terms of its quality and applicability for injection. Firstly, there was low crystallinity and, consequently, low purity. It was also quite hygroscopic and yellow colored. Administration via injection was also found to be very painful.

In contrast, SM-HCl-CaCl₂ showed high crystallinity, high purity, no coloration, and was less painful than streptomycin trihydrochloride for injection purposes. The production processes of SM-HCl-CaCl₂ were covered and monopolized by the patents of Merck & Company. Therefore, a Japanese company who wished to produce the complex salt had to make a special contract in order to gain exclusive license. The contracting party was also able to use the carboxylic cation exchange resin, Amberlite IRC-50, in the purification steps of streptomycin and commercially produce the synthetic derivative dihydrostreptomycin.

In the “Minimum Requirements of Streptomycin” released on the 20th of December 1949, the standards for streptomycin trihydrochloride were specified to 1) contain not less than 300 μg (potency)/mg, 2) be sterile, 3) be non-toxic, 4) be non-pyrogenic, 5) be free from histamine or histamine-like depressants, 6) contain not over 3% moisture, 7) have a pH between 4.5-7.0, and 8) be transparent in aqueous solution at 0.2 g/mL. Thus, the purity of streptomycin trihydrochloride salt was set to be equivalent to 35.6% or above (when calculated based on 842 μg (potency)/mg being equal to a theoretical purity of 100%). The imported SM-HCl-CaCl₂ made by Merck & Co. contained approximately 650 μg (potency)/mg, equivalent to a purity of around 83.4% (with 779 μg(potency)/mg being equal to a theoretical purity of 100%).
After intense negotiations, two companies, Meiji Seika and Kyowa Fermentation, reached agreements for the establishment of individual contracts with Merck & Co. in February. Their introduction of foreign technology was approved by the Japanese Government on the 12th of April 1951. In Meiji Seika, both quality and productivity of streptomycin were remarkably improved by the processes covered in the contract. The company started production of dihydrostreptomycin in April of 1953, to replace the market use of SM-HCl-CaCl2. As the result of such contracts, collaborative research on streptomycin conducted among pharmaceutical companies in the PD-RCS was terminated. The companies excluded from the contract with Merck & Co., namely Kaken, Nikken Chemical and Shimane Chemical (merged to Sanyo Pulp in June of 1951), continued streptomycin production by means of their own independent processes.

With the technology and knowledge being introduced from the USA, the production of streptomycin preparations at Meiji Seika and Kyowa Fermentation increased very rapidly. As noted in our previous report, domestic production reached amounts enough to satisfy national demand. As a result, the import of streptomycin from the USA was discontinued in 1953 and that of dihydrostreptomycin in 1954.

As seen in Fig. 1, a variety of preparations, namely streptomycin trihydrochloride, SM-HCl-CaCl2, sesquisulfate salts of streptomycin, dihydrostreptomycin, dihydrodesoxystreptomycin, and a combination of streptomycin and dihydrostreptomycin, were used clinically in Japan. However, only streptomycin sesquisulfate remains currently in use, due to adverse reactions associated with
the other compounds.

6. Exemption from royalties on the streptomycin patent

Following a request by Dr. Waksman in 1946, Merck & Co. transferred basic patent rights on streptomycin to the RREF. The rights had been in possession of the company under a 1939 agreement. However, Dr. Schatz, the co-discoverer of streptomycin, in March of 1950, brought a lawsuit against Dr. Waksman and the RREF for receipt of some portion of the royalties. The case was settled in December of 1950, but Dr. Waksman and the RREF had a very difficult time throughout the year defending against the lawsuit. It was uncertain as to why the RREF did not request royalties on the patent for five Japanese companies who were involved in streptomycin production. Hence, it is unknown whether or not the lawsuit or courtesies from Dr. Waksman played any contributing roles.

In the midst of such confusion, around the end of September 1950, Dr. Yusuke Sumiki, a board member director of the JPRA, visited Rutgers University and asked Dr. Waksman to support the Japanese microbiologists in their research efforts and studies abroad. Responding to the request, Dr. Waksman proposed that his share (10%) of the royalty on streptomycin be waived with the hope of promoting antibiotic research in Japan. Upon his return from the USA, Dr. Sumiki negotiated intensely with the Directors Board of the JPRA, the MHW, the Science Council of Japan, and GHQ/SCAP to establish a research organization to manage the funds to be raised as a portion of the royalties from streptomycin in Japan.

Dr. Waksman visited Japan in December of 1952 on his return home from Stockholm, where he had just received the 1952 Nobel Prize in Physiology or Medicine. The purpose of his visit to Japan was to deliver a lecture for the centennial celebration of Dr. Shibasaburo Kitasato’s birth, in response to an invitation by the Kitasato Institute in cooperation with Keio University School of Medicine (established by Dr. Kitasato, in 1917). During his stay, Dr. Waksman also visited several microbiology laboratories throughout Japan and strengthened his intentions to support capable researchers that may be hampered by financial constraints. Building on the momentum of this visit, the Waksman Foundation of Japan was established in November of 1957, with the aim of supporting and encouraging academic research on microbiology and medicine. Word was handed down that Dr. Waksman was very much impressed with the quality of the domestically produced streptomycin in Japan, containing not less than 650 μg (potency)/mg (81.5% pure or higher). This was as stipulated in the “Minimum Requirements for Antibiotic Preparations” enacted in March of 1952, nine months before Waksman’s visit (taken from Dr. Hamao Umezawa’s personal communications).
III. Discussion

Japanese people have a racial tendency to be highly susceptible to tuberculosis, irrespective of average lifespan. Based on the WHO global tuberculosis database, incidences per 100,000 population in 2014 were 3.1 in the USA, 5.2 in Canada, 6.0 in Italy, 6.2 in Germany, 8.7 in France, and 12.0 in the UK (including North Ireland). In Japan, however, it stands at 18.0. Even now, among developed countries, the extraordinarily high incidence of those suffering from tuberculosis in Japan is widely recognized.

Thanks to streptomycin therapy, the tuberculosis mortality rate (per 100,000 population) had fallen dramatically within only five years, from 187.2 in 1947 to 82.2 in 1952. Although several cases of original Japanese research on streptomycin progressed since 1947, the support of the PHW and GHQ/SCAP was necessary in order to achieve production of sufficient amounts to fill domestic demand and control the much-feared national disease tuberculosis.

In this study, the authors investigated and analyzed (based on the documents of the PHW and JPRA and other sources) the details of the actions taken by the PHW, under cooperation with GHQ/SCAP and the US Government, to introduce advanced US technology for streptomycin production in Japan. It was also confirmed that the PHW extensively helped Japanese industries in ways that would be inconceivable today. Such examples are the provision of the original streptomycin-producing strains obtained from Dr. Waksman and transfer of expertise in streptomycin production from the principal manufacturer, Merck & Company.

Additionally, the PHW intended to periodically import high quality streptomycin preparations from the USA and distribute them throughout Japan, until domestic production was satisfactory. Best efforts were also made to allot the GARIOA fund for such purchases.

In our previous report, the achievement of domestic streptomycin production was described, along with the scope of the production transitions, production amounts, and quality standards. As a result of this study, it is possible to grasp a much larger perspective regarding the support of the PHW as related to streptomycin production in Japan.

It might be worthwhile, in the research of the history of pharmacy, to know the background of such a rapid achievement of domestic streptomycin production and how the existence of PHW policies greatly influenced the improvement of hygienic conditions in war-torn, occupied Japan.

Dr. Jackson Foster, who contributed greatly to the achievement of domestic penicillin production in Japan, had plenty of experience with industrial scale production of antibiotics produced by soil actinomycetales, at Merck & Co. in collaboration with Waksman’s laboratory at Rutgers University. Therefore, it was inevitable that Dr. Hamao Umezawa obtained, as early as 1947, a streptomycin-like substance from a strain of Streptomyces, after learning about promising prospects of soil actinomycetales and antibiotics produced by Dr. Foster.

Dr. Selman Waksman visited, during his stay in 1952, several microbiology laboratories.
throughout Japan\textsuperscript{63}) and gave guidance on how to isolate, cultivate, and identify actinomycetes strains. Using it as an opportunity, extensive exploratory research was conducted at many laboratories and it resulted in many novel antibiotics being discovered. This time period, the 1950’s - 1960’s, later became known as “The Golden Era” of antibiotic discovery. Among the antibiotics, a macrolide leucomycin (complex) \textsuperscript{64)}, discovered in 1953 by Dr. \textsc{Toju Hata} of the Kitasato Institute, and an aminoglycoside kanamycin\textsuperscript{65)}, discovered in 1957 by Dr. \textsc{Umezawa} of the NIPMH, have been particularly regarded as masterpieces of the era.

Dr. Satoshi \textsc{Ômura} of the Kitasato Institute elucidated\textsuperscript{66}) the macrolide structure of the leucomycin components in 1967 and, thereafter, continued to expand research on macrolide antibiotics. In collaborative research between the Kitasato Institute and Merck Research Laboratories, an epoch-making macrolide compound, avermectin, and its dihydroderivative, ivermectin, were discovered\textsuperscript{67}). By 2014, the antiprotozoal activity of ivermectin, particularly against filarial worms causing river blindness (onchocerciasis) and elephantiasis (lymphatic filariasis), has protected over 480 million African people from suffering from these diseases. For the discovery concerning a novel therapy against infections caused by roundworm parasites, the 2015 Nobel Prize in Physiology or Medicine was awarded\textsuperscript{68)} to Dr. Satoshi \textsc{Ômura}, jointly with Dr. William Campbell of Merck Research Laboratory (currently Drew University, New Jersey, USA).

One may recognize the legacy of antibiotic research that began with Dr. \textsc{Waksman} and eventually continued through many succeeding scientists, like Drs. \textsc{Foster}, \textsc{Umezawa}, \textsc{Tishler}, and \textsc{Boyd Woodruff}, to Dr. \textsc{Ômura} and his colleagues\textsuperscript{67,69}).

\textbf{IV. Conclusion}

As described in our previous report\textsuperscript{60}), the commercial production of streptomycin in Japan was achieved within a short period of time, following that of penicillin. In the background of such success, the active support of the PHW, based on their policies to improve the hygienic status of occupied countries, also existed. In this study, through detailed investigations and analyses, it was confirmed that the introduction of technology and knowledge on streptomycin production from the USA contributed greatly to the achievement of successful commercial manufacturing of streptomycin in Japan.

It is widely known that the domestic penicillin production was successfully initiated by the introduction\textsuperscript{1}) of the US technology through the guidance of Dr. \textsc{Foster}. However, no appropriate document existed displaying the entire perspective of the active support given by Brigadier General Sams for the establishment of commercial streptomycin production in Japan. In particular, his actions to import streptomycin preparations from the USA until domestic production reached an amount satisfactory enough to fill national demand, might be regarded as a form of humanitarian assistance. In fact, it is confirmable from the statistical data\textsuperscript{3}) that streptomycin exerted a great hy-
gienic contribution toward dramatically decreasing the mortality rate of tuberculosis within a very short period of time in Japan.

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我が国において抗生物質医薬品の品質基準の
果たした役割に関する薬史学的・公衆衛生学的考察：
第5報　米国からのストレプトマイシン製造に関する
技術と知識の移入†

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我が国において抗生物質医薬品に係る品質基準が果たした役割を、薬史学的に検証し公衆衛生学的に解析するために、ストレプトマイシンの製造に関する技術と知識を米国より移入した経緯を調べた。本研究により、それらの移入は連合国軍総司令部の公衆衛生局長であったクロフォード・サムス准将が、厚生省を通じて行った強力な支援によることが確認された。ストレプトマイシンの発見者であるセルマン・ワックスマン博士も、メルク社の研究者たちと協力し、同局を通じて日本の企業にストレプトマイシンのオリジナルの生産菌株を供与し、ストレプトマイシン製造に関する専門的知識や技術を移転するなどの援助を与えている。

米国より導入した技術と知識により、国内のストレプトマイシン製品の製造は急速に増加した。前報に記述したように、国内生産量は3年間のうちに、国内需要を十分に満たすまでに達している。日本国民は民族的に、不治の国民病として知られていた結核に対して感受性が高い傾向がある。ストレプトマイシンの導入により、1947年には人口10万対187.2であった結核死亡率が、1952年には82.2へと急速に低下した。

†本論文を、1946年（昭和21年）8月26日に設立された「日本ペニシリン学術協議会（財団法人日本抗生物質学術協議会を経て、現在は公益財団法人日本感染症医薬品協会）」の70周年に際して、我が国における抗生物質研究の先駆者に捧げます。