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A Year's Struggle: How Japan Is Recovering Damaged Generic Supplies After Quality Violations

Group Points To Pricing Risks

by Lisa Takagi

Japan struggles to recover its ever-expanding supply chain for generic drugs after several key players had their production stopped because of a series of GMP violations. As the share of generics grows under government policy, some in the industry argue the problems are deeply rooted in a decades-old pricing system.

The Japanese government and associations of domestic firms are trying to improve quality control and bring back stable distribution to the generics sector.

While the country has almost reached its volume share goal of 80% to reduce ever-rising healthcare costs, a supply shortage triggered by quality violations exposed in several generic firms has impacted patients and healthcare providers for over a year.

“We receive a prescription for a generic drug. It’s out of our stock. We have no choice but to spend extra time and effort asking (both the patient and the doctor) if we can provide a non-generic alternative. Can’t we put an end to this (cycle)?” tweeted a pharmacist in Japan on 16 March 2022 with a crying emoji. The post quickly gained more than 180 likes.

Posts like hers haven’t been rare in the country since the beginning of 2021. Japan reimburses around 13,000 drugs under its national health insurance system, but the supply of more than 3,000 has been impacted, with 743 of these out of stock by September 2021, according to a report submitted to the government by the Federation of Pharmaceutical Manufacturers’ Associations of Japan.

Although the government has been cautiously monitoring the supply chain and asking generic firms to recover this gradually, 82 products were still out of stock as of 12 April 2022, shows a list maintained by the Japan Generic Medicines Association (JGA).

QC Violations, Deaths, Distribution Crisis

The confusion in the supply chain started in December 2020, with the contamination of the oral antifungal Meek (itraconazole) from Kobayashi Kako Co., Ltd. with a high dosage of the hypnotic drug rilmazafone in the manufacturing process. Two patients receiving the product died and negative symptoms including dizziness and fainting occurred in 245 patients, of which 38 people had traffic accidents, according to the company's official website updated in March 2022.

Investigations by Japan's Pharmaceuticals and Medical Devices Agency and the local government triggered recalls of 30 products by Kobayashi Kako and six drugs from other generics firms including *Aska Pharmaceutical Company Limited*, *Meiji Seika Pharma Co., Ltd* and Elmed (previously known as Elmed Eisai), for whom Kobayashi Kako had been acting as a contract manufacturer.

After the incident, a series of investigations of manufacturing plants of generic firms all over the country by authorities ended up exposing violations of good manufacturing practice (GMP) by several domestic manufacturers. This led to several plant suspensions issued to major players; *Nichi-Iko Pharmaceutical Co., Ltd.* in March 2021, *Choseido Pharmaceutical Co. Ltd.* in 2021 and Kyowa Pharmaceutical Industry Co., Ltd in March 2022 over the use of undeclared materials and processes during production. (Also see "*Nichi-Iko Suffers After Plant Closure*" - Generics Bulletin, 28 May, 2021.) (Also see "*Nichi-Iko Resumes Production After Suspension*" - Generics Bulletin, 12 Apr, 2021.)

Nichi-Iko Manufacturing Plant Raided Over Illegal Production – Report

By Dean Rudge

30 Mar 2021

Japanese generics giant Nichi-Iko had a key manufacturing plant raided by Japanese authorities and regulator the PMDA, per media reports, following the recent suspension of production and sales at the site in the Toyama prefecture.

Read the full article here

The impact was high. Under a policy to encourage the consumption of generics to contain healthcare costs, Japan doubled its volume share of such drugs from 2005 (32.5%) to 2017 (65.8%). According to the latest market report by the ministry of health, labour and welfare (MHLW) released in December 2021, that share had risen to 79%. Today, the MHLW is holding to its generic volume share goal of “80% by 2023” (the end of fiscal 2023 in March 2024).

What Caused The Long-Lasting Issues?

On the other hand, GMP violations had already become an issue in the 2010's after several violations were exposed, although the MHLW had tightened its regulations on drug manufacturing and its quality control. For companies like Kobayashi Kako and Nichi-Iko, the pressure to keep their expanding production lines running with low costs won out over compliance, according to their investigative reports.

Kobayashi Kako coincidentally had expanded its manufacturing capacity more than 20 times from 2000 to 2019 and had issues in staff training and human resource planning which caused failure in quality management, according to an investigation report released in April 2021.

The report points out the company had several internal checkpoints in its manufacturing process intentionally skipped or mended, sometimes covered with false records. A couple of contaminations found before the rilmazafone incident were unreported or overlooked by busy plant staff to keep production on schedule. Although management was aware of the issue, reporting of updates to manufacturing processes to authorities were outweighed by other tasks to cut the manufacturing cost, the report states.

Another report from an external investigation of Nichi-Iko states the company had a similar situation. Internal warnings from staff who witnessed the illegal re-processing of unqualified materials had been ignored under pressure to supply products on schedule.

"The current pricing system and distribution were obviously the distant cause of those serious GMP violations," states a document released in February 2022 by the Japanese Society of Generic and Biosimilar Medicines in response to the generic crisis, although it condemns the management of the companies involved in violations.

Because Japan reimburses drugs' official prices to pharmacies and hospitals, there is a practice between these buyers and pharmaceutical companies to hold the real price lower than the reimbursement level for the buyers' benefit. Because the official prices of generic drugs are low from the beginning, pressures on generic firms to cut down the price and unit production cost – often in the manufacturing or distribution process - tend to be high, which could risk stable supply, the research states.

Business And Bureaucratic Effort Needed

After the series of incidents, both the government and associations of generic firms have made efforts to recover the stable distribution of generics while maintaining quality and safety.

The MHLW has listed 506 chemicals to be guaranteed stable supply for healthcare providers while closely monitoring the market. In December 2021, the ministry requested domestic pharma firms to lift the stock controls on 130 products; it is even planning to slightly raise or maintain

prices if necessary, according to an explanatory document released in March 2022.

The local associations of generic firms are also enhancing their watchdog scheme to recover public trust in the market. In January 2022, the JGA ran self-checks of manufacturing plants belonging to 38 member companies by a third party, which found 31 out of 38 members, and 1,157 products out of 7,749, needed the re-filing of manufacturing processes to authorities, although association stated all the tested products' quality matched the legal criteria.

A Japanese Society of Generic and Biosimilar Medicines' proposal to prevent the reoccurrence of GMP issues lists three topics to focus on: enhancement of internal governance by pharma; tight GMP audits by authorities; and more reasonable pricing for generic drugs.

Suggesting tighter governance in pharma, the organization calls for "review and revision of current legal systems in drug pricing and distribution."

"Now that the share of generic drug is increased, it's inevitable to create systemic infrastructure to secure generic firms' production and (supply of) generic drugs as a social asset," it states.

A year after the Kobayashi Kako incident, Sawai Group Holdings, the parent of Japanese generic major *Sawai Pharmaceutical Co., Ltd.*, announced the acquisition of Kobayashi Kako's production team to establish a new company, Trust Pharma Tech, a transaction completed on 31 March 2022.

The announcement states Trust Pharma Tech "will work on enhancing its compliance and quality control system to start shipping products in April 2023." (Also see "*Sawai To Take Over Facilities Owned By Scandal-Hit Kobayashi Kako*" - Generics Bulletin, 6 Dec, 2021.)