Inappropriate testing investigation results and recurrence prevention measures

Summary of inappropriate testing incident

Teprenone Capsules 50mg "Sawai" produced at Sawai Pharmaceutical's Kyushu Factory always undergoes dissolution tests as part of stability monitoring to continually check and guarantee post-approval quality. The same type of tests conducted in April 2023 revealed that previous testing had been conducted inappropriately.

The products, drugs to improve acute gastric mucosal lesions during the acute exacerbation phase of acute and chronic gastritis and to treat gastric ulcers, can be used for up to three years after production. The dissolution test uses the paddle method, in which the formulation is added to a specific test solution, mixed, and then the volume of dissolved drug is measured. As a general rule, the test is conducted one year, two years, three years, and four years after production. The passing standard is a dissolution rate of 70% or more, and a result of less than 70% is out of specification (OOS).

In the improper tests, the granules were removed from the capsule and placed in a different capsule, and then the refilled specimen was subject to a dissolution test to determine whether it passed or failed. Capsule aging is the reason for the decline in dissolvability. Therefore, refilling new capsules with the content of old capsules would not result in the decline in dissolvability and make it possible to avoid a non-compliant test result.

After the misconduct was discovered, an internal investigation was quickly launched and a special investigation committee, which included independent experts in GMP and attorneys, was established. An investigation of facts related to the inappropriate testing was conducted between July 20 and October 17, 2023, and the special investigation committee submitted their report on October 20 of the same year.

Investigation results

The investigation by the Special Investigation Committee included (i) a detailed review and examination of relevant documents, (ii) interviews with a total of 56 people involved, (iii) access to the testing facilities, (iv) a digital forensic examination of high-performance liquid chromatography data and internal email data related to the dissolution tests of this product, and (v) a questionnaire survey.

As a result, it was found that the inappropriate testing was conducted following an out-of-specification (OOS) result in a dissolution test during stability monitoring conducted in 2013.

In response to the OOS results, the senior management of the Kyushu Factory at the time ordered the capsule content to be transferred to new capsules and tested to examine the cause of the decline in dissolvability. However, they did not issue an internal report, examine the cause, and take corrective measures in accordance with GMP.

After that, test staff thought that senior management had provided instructions to handle the situation by using specification results based on tests of the replaced capsules, which resulted in this inappropriate testing continuing.

Although it was not found that senior management had directed or implicitly approved the inappropriate testing, due to inadequate supervision, inappropriate testing practices were not detected and continued for many years. It was found that at least since the third-year dissolution test of this product in 2017, there had been inappropriate testing conducted for all lots, and that for those falling outside of specification results in the dissolution tests from 2010 to 2014, proper deviation management based on GMP had never been carried out until the inappropriate testing was discovered.

The investigation notes the following human factors for why this situation continued: (1) the widespread tendency to underrate the importance of stability monitoring, (2) the tendency not to question but simply follow superiors' instructions, and (3) lack of understanding of GMP among those involved in the testing. In addition, there were several physical factors for the incident (1) defects in the effective supervising system in terms of quality control and quality assurance, (2) insufficient management of test records, and (3) excessive workload and shortage of members of the Quality Control Department, which is responsible for the test.

Details of the latest initiatives related to recurrence prevention measures can also be found on the Sawai Pharmaceutical website, under "Progress with the Corporate Culture Reform Project."
https://www.sawai.co.jp/important_news/detail/17(Available only in Japanese)

Main recurrence prevention measures

Corporate Culture Reform Project

Main topics	Initiatives	Implementation status and frequency
Thoroughly spread a spirit of legal compliance and general compliance through retraining and routine notices	Designate a legal compliance week (in general, third week of each month) and provide all employees, including directors, with compliance education on the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices and the GMP basics	Once a month (legal compliance week)
Strengthen promotion of the whistleblowing systems	Improve understanding of the whistleblower system, such as thoroughly educating employees that such items as GMP violations can also be reported using the system	As needed
Create a venue for direct dialogue between the president and employees and promote dialogue between management and employees by regularly issuing the messages from the president	Create venues for direct dialogue between employees and responsible directors, including the president, which involves holding town hall meetings	At least once a month (as needed)

Manufacturing Division

Main topics	Initiatives	Implementation status and frequency
Reconduct and continue to conduct GMP education for all employees	Hold group discussions at each workplace (educate employees about this incident and uncover issues for each department they work in) Obtain the opinion of all employees regarding discussion items in order to rebuild a quality culture	Work to resolve the following issues taking into consideration employee opinions
Secure human resources for the factory Quality Control Department and Quality Assurance Department from either inside or outside the company	Redefine the number of staff required, strengthen recruiting activities, conduct job rotation of experienced employees	Plan to add about 105 employees by fiscal 2026
Introduce a system to ensure data integrity	Quickly introduce MES and LIMS into all factories (already introduced: Kashima, Kanto, Sanda Nishi [MES], TP Seima, TP Yachi [LIMS])	Introduce into the new building of Daini Kyushu Factory in June 2024

Kyushu Factory

Main topic	Initiatives	Implementation status and frequency
Create a system to allocate necessary resources to the Production Department and Quality Management Departments	(1) Undertake a planned increase in number of employees* (2) Ensure integrated data management and data integrity by introducing chromatography data systems (CDS)	(1) Plan to add 18 employees by the end of fiscal 2024 (2) Completed introduction by June 2024
Continue to conduct legal compliance education and training	(1) Offer all employees a total of 40 GMP educational (e-learning) courses (2) Repeatedly provide employees with GMP education (30 basic classes) for the term of their employment	(1) Completed May 2024 (2) 10 classes/year, one cycle every three years

* The reference rate based on the Approach Toward Securing Workers for Manufacturing Sites set by the Federation of Pharmaceutical Manufacturers' Association of Japan's Quality Committee has already been met

Reliability Assurance Division

Main topic	Initiatives	Implementation status and frequency
Obtain quality event information in a timely manner from manufacturing sites by digitalizing information and ensuring data integrity	(1) Introduce a quality event management system (QMS) (jointly with the Manufacturing Division) (2) Introduce MES and LIMS (jointly with the Manufacturing Division)	April 2025: Launch deviation and CAPA operations by QMS
Construct a verification system based on legal compliance by third parties regarding decisions of the responsible director and Marketing Director of the Pharmaceuticals	(1) Have Audit & Supervisory Board members attend monthly meetings when the Marketing Director of the Pharmaceuticals (2) Have outside experts attend meetings when the responsible director reports to the Compliance Committee	(1) Once a month (2) Monthly