

Receipt of Complete Response Letter from FDA for STN1011700 (Q&A)

Q1-1:

The first question is about the development of your company's products in the US. Unfortunately, there have been no cases where approval has been granted by the PDUFA in a straightforward manner, and I am a little surprised that the GMP issue came up just before the PDUFA. Are there organizational issues related to applications and regulatory affairs, or communication problems with the authorities? Or was it just bad luck? Please let me know if this area can be improved in the future as you gain more experience.

A1-1

Taniuchi: Let me answer. First of all, thank you for your question and for pointing it out.

As I mentioned earlier, this situation was unexpected due to the vendor's situation. In that sense, I think there was an element of bad luck.

On the other hand, the US system is now being strengthened, and we are aware that we are making progress, so we would like to get results firmly.

Peter, could you comment a little more?

Sallstig: Thank you for your question.

The first thing we would like you to recognize about STN1011700 is that the result of the clinical study we applied was accepted. The issues pointed out this time are related to GMP, and are unexpected and out of our control.

However, we are taking this matter very seriously, and we are now doing our best to work closely with the CMO and the FDA to resolve this matter as soon as possible. I believe that we have been able to strengthen our organization, as evidenced by the fact that *Verkazia* has been approved in the US.

This issue was unrelated to the development of STN1011700 or the product itself, but was related to GMP, so we will do our best to solve the problem as soon as possible, and deliver the medication to patients as soon as possible.

Q1-2:

The President mentioned that there will be no major impact on the MTP2025, but if there is a delay in the approval date in the future, or if there is a prospect, will there be an update on the numerical targets?

A1-2

Taniuchi:

In any case, regarding the approval date, as Mr. Kimura mentioned earlier, there are a number of factors that need to be taken into consideration first. After that, when the schedule and other conditions for approval become clear, we would like to provide more specific updates on the status of sales and the US business at that time.

Q2-1-1:

I also find it a little difficult to see the extent of this GMP issue from the outside, so I would like you to explain it a little more, as far as you can.

You commented earlier that the GMP issues have been mostly identified, but how difficult do they seem to be solved? Also, how long will it take – at least 6 months in your time frame, or like a year? Please explain about that as much as you can at this point. Thank you.

A2-1-1:

Kimura: Thank you for your question. I will reply to you.

First of all, as I explained, this GMP issue was pointed out during GMP inspections of other companies' products, so we would like to refrain from disclosing details of the issue.

As for how long it will take, as Peter mentioned earlier, we will be discussing and collaborating with the CMO and the FDA, and we would like to proceed with the project on the earliest possible timeline. However, to be honest, it is not yet clear how long it will take.

I apologize for the repetition, but I would be happy to update you on the details during the financial results briefing in February next year.

Q2-1-2:

By the way, what is the issue? Is it difficult to say anything about it right now, including whether it's something that could be solved with time, or something that might be quite difficult?

In short, if the issue is difficult, I think that approval is still difficult at this point. However, if the issue can be resolved with time, we can expect approval at some point.

A2-1-2:

Kimura: Let me answer.

Basically, GMP issues are clearly presented by the FDA, and there is a process for companies and CMO, or manufacturing facilities, to take corrective actions. Basically, regarding the difficulty of the GMP issues, I understand that they can be basically solved, although it depends on the degree.

Q3-1:

The first is that you mentioned earlier that it was bad luck, and that is fine for a conclusion, but I would like to have a more solid explanation.

I think it is the responsibility of the manufacturer and distributor to inspect and evaluate the quality control system of the contractors before entrusting the product to them. Was there any problem with such a system in your company?

I don't think you can tell us the specifics of this, but I'm wondering if other vendors can say, "If you ask that vendor to do that, you'll get in trouble." Or is the event in question something that can be said, "Santen can't see through?"

A3-1:

Taniuchi: Thank you very much. First, I will answer this, and then Mr. Kimura will give you some additional information.

First of all, of course, we conduct due diligence and inspections on contractors. And this time, this is caused by a different part, a different product from our product. In a sense, our production line is different from theirs, so to be honest, we would like you to understand that we are doing the best we can in this situation.

Mr. Kimura will share some details with you.

Kimura: Let me give a supplementary answer.

As Mr. Taniuchi mentioned, of course, due diligence is conducted from various perspectives in order to select the contractors. As for quality in particular, as you may have just asked, our quality assurance experts audit and check the site before selection.

However, these audits are naturally limited to the areas that we outsource, and we are not able to conduct audits of areas that manufacture products for other companies. I don't think this is limited to our company.

In addition to our own evaluation, for example, this contractor is a leading CMO company in the US and globally, and in the US, for example, we are able to objectively collect information on the FDA's inspection history. In the process of selection, we judged that there would be no problems in the past inspections and selected them.

You also pointed out why we chose such a company, but as I mentioned earlier, this contractor is a leading company, a leading class CMO, so I understand that not only our company, but also many other pharmaceutical manufacturers are using this contractor.

Taniuchi: So, the result is the result, but we would like you to understand that we did everything we could in advance in the process, and also the production line was different from ours, so we could not have done to that extent. However, we will take the results solemnly, and as Peter mentioned earlier, we will work closely with them.

Q3-2:

In addition, the second item on page 6 says that communication is necessary, including some other matters, but are some other matters not critical?

Will the timing of the reapplication be mostly determined by this issue of the contractor? Do we hardly need to worry about the delay due to the other matters not being resolved when the contractor's issue has been resolved?

A3-2:

Morishima: I will give you an answer.

As for the issues other than GMP pointed out in the CRL, we have not yet reached the final approach, so there are still some details to be worked out, such as the contents of the package insert and communication with patients. However, as I said in my explanation at the beginning, there are no major issues, no major hurdles for approval. We are aware that we will have to work out the small details and communicate with the FDA to finalize the process.

Q4-1:

What kind of changes will be made to future efforts in response to this, including your thinking about hedging risks? For example, is it possible to outsource to multiple companies, or to have your domestic plant certified by the FDA?

A4-1:

Taniuchi: Thank you for your question.

As you said, we are learning from these results, and we are still discussing the possibility of re-examining vendors and backing them up for future projects.

We are also making capital investments in the Shiga building and Suzhou Plant, and 1 of our objectives is to acquire the capability to comply with cGMP in the US. In the long term, we plan to raise the overall operational capacity of the Company. Until then, we will continue to work on this issue over the long term, even though it happened this time.

Q5-1-1:

I have 1 question, including confirmation, about the contractor. I understand that you can't tell us the details because it's about the other party, but as a matter of fact, is there something like a warning letter issued by the FDA to this contractor? Since this is a confirmation of facts, I'm sure you can answer without mentioning the other party.

A5-1-1:

Kimura: Let me answer.

Whether or not a warning letter has been issued is also related to the details of the inspection observations. In the end, it comes down to the specifics of which class it applies to, so I'd like to refrain from disclosing that. Thank you for your understanding.

Q5-1-2:

From a common-sense perspective, it's issued, isn't it? Since this is non-compliance with GMP, is it okay to recognize that it is issued, although you may not know if it is for the production line or the whole plant?

A5-1-2

Kimura: In the case of the FDA, there are 3 categories for pointing out: no action required, or voluntary improvements needed. And the other is the final mandatory pointing out, which is equivalent to the warning letter that you mentioned. Regarding whether a warning letter has been issued or not necessarily, or what criteria it is on, I'd like to refrain from commenting on that.

Q5-1-3:

I understand. In any case, it will be updated as of Q3, but this is also up to the other party.

A5-1-3:

Taniuchi: I would like to add something.

Since this is a story about another line of another company's product, we would like you to understand that we can't talk too much about it.

On the other hand, we have heard from them that they are working hard to deal with this situation. Regarding the results of their efforts for the other medication, assuming it is oral medication and they are experiencing the problems, we are naturally communicating with them on a daily basis about what is going on now.

If there is any progress by February regarding whether they have already responded, or how the authorities perceive the situation and how they have responded, we would like to talk to you again in February or, of course, hopefully sooner when we can say.

As for the issue itself, since we are a third party, we would like to refrain from discussing the details.

Q5-1-4:

I understand. I know enough. Since this time was also like a car accident, I hope you will do your best.

A5-1-4:

Taniuchi: Thank you very much. Thank you for your understanding. We will do our best.

[END]