

## Orphan Drug Talks and Midnight Meetings Under Japan-EMA Collaborations

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When Junko Sato, Japan's international liaison officer at the European Medicines Agency in London, started trying to convince her regulatory colleagues back home to expand the scope of the discussions they have with their EU counterparts on drugs for treating rare diseases, she had her work cut out.

Regulators at Japan's Pharmaceuticals and Medical Devices Agency and at the EMA were already discussing and exchanging information on orphan drugs through teleconferenced "cluster" meetings when Dr. Sato was seconded to the EU agency by the PMDA in May 2012. However, these meetings only dealt with drugs that had already received orphan designations in both regions. Dr. Sato believed it was crucial that EMA-PMDA collaboration should also cover orphan drugs that are at the pre-designation stage. Co-operation between both agencies earlier on would be especially useful for multi-regional development in the orphan drugs space, where the number of patients with rare diseases is limited, she told *Scrup Regulatory Affairs*.

The PMDA was at first reluctant to expand discussion to pre-designated drugs, Dr. Sato

said. "As you know, [orphan drug] designation in Japan [in contrast to the EU] requires clinical data." One of Japan's designation criteria requires companies to explain the rationale for their drug development "based on existing non-clinical and clinical data in the latter half of the Phase I study or in the first half of the Phase II study, except when the product has already been approved overseas or sufficient clinical study data are available," she explained. This requirement means that the timing of a designation in Japan lags behind that of the EMA. On the other hand, it also makes the likelihood of being granted a designation higher in Japan than in EU, Dr. Sato noted. Because of this difference in criteria, "my PMDA colleagues hesitated to expand the discussion to pre-designation," Dr. Sato said.

Convinced that orphan designation was a "formality" that should not stand in the way of broadening discussions, Dr. Sato set about negotiating with the PMDA on the matter. Getting the PMDA to change its mind was no easy task, Dr. Sato indicated, adding that this has been her biggest challenge as liaison officer. But her efforts paid off. A few months ago, her "PMDA colleagues agreed

to expand [discussions] to pre-designation." "I believe this expansion will help patients with rare diseases," she said.

Dr. Sato spoke to *Scrip Regulatory Affairs* following a presentation she gave at the 26th annual DIA EuroMeeting, in Vienna, in March, on the current status and challenges of the bilateral and multilateral meetings that the PMDA and Japan's Ministry of Health, Labour and Welfare conduct with their international counterparts. Japan's bilateral and multilateral initiatives seek to leverage the human, scientific and financial resources – and the knowledge and experience – of other key regulatory authorities so as to "avoid duplication of effort, make our activities more efficient and... allow us to focus our limited resources on higher-risk areas of concern," Dr. Sato said.

The bilateral and multilateral communications are conducted under confidentiality arrangements that the PMDA/MHLW has with 11 regulatory agencies around the world – in Australia (TGA), Brazil (ANVISA), Canada (Health Canada), the EU (European Commission / EMA), France (ANSM), Ireland (IMB), Italy (AIFA), Singapore (HSA), Switzerland (Swissmedic), the UK (MHRA), and the US (FDA). The PMDA/MHLW is keen to establish confidentiality arrangements with even more countries/regions as part of its

international mission to reduce the burden of regulation and harmonize regulatory requirements.

### Fruitful and timely exchanges

Dr. Sato sees Japan's international liaison system as "one of [the PMDA's] key tools" for enhancing bilateral communication. In addition to having a liaison officer at the EMA, the PMDA/MHLW has a liaison officer posted at Swissmedic and it is planning to dispatch an officer to Health Canada "shortly". Discussions are also under way to replace the liaison officer that had served at the US Pharmacopeial Convention (USP) between 2009 and 2013.

Dr. Sato is the second liaison officer to be sent to the EMA under the PMDA/MHLW-EMA confidentiality arrangement. The secondment was for two years and it will come to end on 11 April, after which Dr. Sato will return to the PMDA in Japan; before moving to London, Dr. Sato worked in the PMDA's Office of New Drug and Office of Safety in Tokyo. Her successor at EMA will be Yoshihiko Sano, from the MHLW.

Reflecting on her performance as Japan's "front-line staff of communication" at the EMA, Dr. Sato says she has exchanged "fruitful information" in a "timely manner." "I am proud of this," she commented.

Dr. Sato's role as liaison officer has been "to help co-ordinate PMDA/MHLW activities in Europe relating to the regulation of medicinal products." This has involved enhancing collaboration between the EU and Japanese regulators by providing information from the PMDA/MHLW to the EMA and vice versa. Dr. Sato has also promoted personnel exchange, explored and set priorities for specific areas and topics of interest, and developed new collaboration areas.

### Midnight clusters on oncology

Encouraging scientific dialogue is an important part of the liaison officer's work. Here, for example, Dr. Sato was instrumental in convincing the PMDA/MHLW to join an oncology cluster that the EMA had set up with the US Food and Drug Administration. There are five other clusters at the EMA in which the Japanese regulators participate: advanced therapy medicinal products, nanomedicines, pediatrics, pharmacogenomics and pharmacovigilance.

The PMDA was initially reluctant to take part in the oncology cluster. Dr. Sato had asked her colleagues to participate in this grouping at the beginning of her secondment, but the PMDA declined. The Japanese regulators reasoned that because the products that were being discussed in the cluster had not yet started development in Japan, participation would not be helpful to them.

In addition, the time at which meetings took place was "terrible for Japan," where it would be midnight.

Dr. Sato felt, however, that even if a drug was not being developed in Japan, participating in discussions on the product would be "very helpful" in understanding requirements in each region. One year after first asking the PMDA to take part in the oncology cluster, the liaison officer asked her colleagues again. This time, "with some negotiation," she was successful and Japan joined the oncology cluster.

With regard to her efforts to facilitate harmonization, Dr. Sato gives as an example comparative tables that she is helping to provide on orphan drugs. These tables will compare regulatory requirements and timeline/steps from peri-orphan designation to post-approval. They will be "very helpful" for the regulators and also for orphan drug developers, she said.

Liaison officers are also charged with clarifying the regulatory context of domestic events. One example of how Dr. Sato has met this objective relates to the concerns that arose in Japan last year over a possible association between the use of the human papillomavirus (HPV) vaccines and widespread pain. The Japanese press release on the matter was "very vague," Dr. Sato said. It suggested that HPV vaccines had been withdrawn in Japan, she explained,

adding that this was not the case. "I explained the real situation to the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) and responded to each query from the EU member states."

### Reducing regulatory burden

As for how the liaison officer has contributed to reducing regulatory burden, Dr. Sato highlights as examples English translations of two documents relating to orphan product regulation in Japan that were published on the MHLW website during her secondment. The first document provides an overview of Japan's orphan drug/medical device designation system. The second document, which she expects will be "especially helpful," contains instructions on how to fill out an application for orphan drug designation.

In addition to taking part in cluster meetings, the MHLW/PMDA and EMA interact in a variety of other ways. The agencies have "routine exchanges" in which they inform each other of the safety concerns they have over a medicine and the measures they might be taking. During ad hoc exchanges, they seek each other's opinion on individual marketing authorization applications and on drugs that are the subject of a scientific advice procedure.

They also hold ad hoc meetings to discuss concept papers and draft guidelines that are

under development. It is important for both agencies to share each other's perspective before finalizing these documents, Dr. Sato said. Multinational drug development is increasing in Japan, and if there are too many differences between the Japanese and EU regulations in terms of such things as trial requirements or different primary endpoint, this will oppose a "big problem" for drug developers.

The PMDA is also intensifying its collaboration with the EMA on inspections. Japan and the EU have a mutual recognition agreement on good manufacturing practices (GMPs) and PMDA inspectors participate in the EMA's GMP inspectors working group. Also, PMDA good clinical practice (GCP) inspectors participate as observers in EMA GCP inspections. According to Dr. Sato, the PMDA has recently started to become more heavily involved in both these areas.

Between 2011 and 2013, the number of interactions between the PMDA and the EMA increased year on year, with an average of 40-50 interaction cases per month.

Reflecting on her two years at the EMA, Dr. Sato considered what makes a good liaison officer. It is important to provide "speedy" responses, she said. For instance, "where it was necessary for me to translate a Japanese document before I could deliver a full response, I would submit an executive summary immediately and send more detail

later" on. As a liaison officer, Dr. Sato is not responsible for translating Japanese assessment reports for marketing authorization applications. However, the PMDA, as part of its roadmap for an international vision, is working on translating its regulatory review reports for medicinal products into English.

When requesting information from the EMA, Dr. Sato said it was important for a liaison officer to give the EMA background

information relating to her questions because "it is... very important to obtain appropriate answers."

Finally, it is "extremely important" to remember to provide feedback to the information provider. "Usually people tend to forget [to give] feedback," Dr. Sato said, "but information providers like to know how [their] information was utilized."

*References for this article are available upon request.*