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Directorate

Report on interactions between the Japanese Ministry of Health, Labour and Welfare (MHLW)/Pharmaceuticals and Medical Devices Agency (PMDA) and the European Medicines Agency (EMA)

November 2009 - September 2011

Executive summary

EU and Japan's longstanding history of a collaborative relationship goes back many years and has developed in the area of human medicines regulation through the GMP Mutual Recognition Agreement (MRA), ICH and bilateral meetings. In 2007 the EU and Japan concluded confidentiality arrangements for a 5 year period. Subsequently Japan seconded a Liaison Official to EMA on a pilot basis in November 2009.

This report covers the period since the appointment of the Liaison Official.

The key activities and achievements during this time include an increase in routine and crisis information exchanges and the development of enhanced interactions in areas of mutual interest. Improved cooperation on orphan medicines is being progressed and the formalisation of the participation of Japanese colleagues as observers in the FDA-EMA cluster on paediatric medicines has been agreed.

During the period from September 2010 to March 2011 MHLW dispatched a 'visiting expert' to EMA who worked with the Orphan Medicines Section, providing a Japanese perspective to Scientific Committees as well as to EMA staff members. In addition, there were several visits to EMA by Japanese officials, and EU officials participated in a number of high-level conferences in Japan. In October 2010 the Executive Director of EMA, the Deputy Commissioner of the US FDA, the Councillor of MHLW and the Chief Executive of PMDA met in Tokyo, where they addressed many policy issues of mutual interest in an informal environment.

The placement of the Japanese Liaison at EMA has been extremely beneficial from the perspective of education, awareness of interaction opportunities and timely communications.

The consolidation of communication and collaboration mechanisms between EMA and MHLW/PMDA continues to be an important tool in addressing public health issues related to human medicines and in



increasing efforts to learn from each others' approaches as well as avoiding duplication and facilitating synergic activities.

1. Introduction

EU and Japan have been collaborating for many years in the area of human medicines regulation. This has included participation by both in the International Conference on Harmonisation (ICH) since 1989, a Mutual Recognition Agreement (MRA) on pharmaceutical Good Manufacturing Practices (GMP) concluded in 2001 and ongoing bilateral meetings.

The European Commission (EC), the European Medicines Agency (then EMEA), the Japanese Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) established confidentiality arrangements in the area of human medicines during their bilateral meeting of 2 February 2007 in Tokyo. This arrangement was built upon the previous cooperation and aimed at facilitating greater exchange of confidential information between the parties as part of their regulatory and scientific processes, both before and after a medicine has been approved.

To further facilitate these information exchanges/interactions between Japan and EU, Japan has also seconded a Liaison Official at the EMA in London since November 2009 as a pilot exercise.

The purpose of this report is to give a brief overview of the key aspects of these exchanges/interactions, highlighting the areas of interest and those that are working well.

Although some multilateral activities involving partners other than EMA and MHLW/PMDA are covered, ICH activities are outside of its scope.

The report is structured as follows: Interactions in areas of interest (section 2), routine exchanges (section 3), ad hoc exchanges (section 4), staff exchanges (section 5), followed by conclusions. Statistics showing the numbers and areas of interactions are presented in Annex 1.

2. Interactions in areas of interest

Since the placement of the Japanese Liaison Official at EMA, interactions have been developed in the following key areas of mutual interest: Advanced Therapy Medicinal Products (ATMPs), Pharmacogenomics and Biomarkers, Paediatrics, Orphan Drugs, Nanomedicines, GMP MRA and GCP. These interactions are classified depending on the parties involved, i.e., bilateral (B = EMA-MHLW/PMDA), trilateral (T = EMA-US FDA-MHLW/PMDA) and multilateral (M).

2.1. ATMPs (T)

MHLW/PMDA and EMA have explored and developed several areas of mutual interest. In the ATMP area, PMDA staff attended EMA's Committee on Advanced Therapies (CAT) Workshop on Stem-cell based Therapies followed by the CAT plenary in May 2010. PMDA provided comments on the draft reflection paper on stem cell-based medicinal products, which were duly considered by the Cell Products Working Party & Biologics Working Party. EU experts (France and Germany) presented the EU ATMP regulation at the PMDA biologics symposium in August 2010. PMDA has proposed possible additional collaboration in the area of cell therapy which is currently under discussion.

2.2. Pharmacogenomics and biomarkers (T)

PMDA has participated in the scientific advice by EU-FDA-PMDA about renal toxicity biomarkers raised by PSTC-NWG (Predictive Safety Testing Consortium-Nephrotoxicity Working Group). In response to applications on non-clinical and clinical parts made by PSTC-NWG in March and April 2011, respectively, scientific advice meetings were held in each region, with participation by other regulatory authorities by phone. Assessors in the three regions provided the meeting minutes and List of Questions to each other.

2.3. Paediatrics (M)

Since 2009, MHLW/PMDA (together with Health Canada) has participated as observers in EMA-FDA's paediatric cluster on a pilot basis. In July 2011, both agencies agreed that MHLW/PMDA's participation during the pilot period was to be viewed as successful. They extended an invitation to MHLW/PMDA to continue participating as observers without any specific time limit. MHLW/PMDA considers that this participation provides the opportunity to consider future perspective of paediatric clinical trial regulation, review and post-marketing safety measures in Japan.

2.4. Orphan medicines(B)

The MHLW/PMDA Liaison Official attended the conference to celebrate 10 Years of the Orphan Regulation in Europe held at EMA in May 2010. MHLW was hoping to promote collaboration on Orphan medicines regulation with EMA; this was enhanced after the visit by the external expert from MHLW to the Orphan Medicines Section of EMA. The expert from MHLW provided information about Japan's orphan medicines regulation which EMA colleagues considered to be very similar to European legislation. MHLW/PMDA and EMA agreed to hold quarterly teleconferences and so far two conferences were held, during which information on orphan designation was exchanged, and it was agreed to publish information on the orphan medicines regulatory system in EU and Japan on each other's public website. Plans to further formalise this collaboration are in progress. Taking this opportunity, it was also arranged to increase communication between EMA's SME Office and MHLW's R&D Division.

2.5. Nanomedicines (M)

Both EMA and MHLW/NIHS experts together with the MHLW/PMDA Liaison Official participate in periodical teleconferences of the Nanomedicines International Working Group. Japanese experts also attended the 1st International Workshop on Nanomedicines hosted by EMA on 2-3 September 2010 where they co-chaired the session with the EMA International Liaison Officer and gave a presentation on Japan's regulation on Nanomedicines. In response to EMA's invitation, an MHLW expert participated in the 4th CLINAM (European Conference for Clinical Nanomedicines) held in Basel in May 2011 where she also made a presentation on Japan's regulation on Nanomedicines. The development of a reflection paper on Block Copolymer Micelles as a major activity of the group in 2011 has been proposed, and is being initiated by Japan in collaboration with EU experts. In addition, a web-sharing training session by Prof. Kataoka, The University of Tokyo, is planned for 29 November 2011.

2.6. GMP MRA (B)

EU and Japan established a Mutual Recognition Agreement (MRA) on GMP on human medicinal products in September 2001. Further preparatory work and joint activities were performed under the supervision of a subcommittee which monitored their progress and met in February 2004. Based on this work, the EC and Japan exchanged diplomatic notes in April 2004 confirming the completion of the

preparatory work under the Sectoral Annex on GMP, which became operational on 29 May 2004 with a restricted scope.

The exchange of information based on the MRA has been leveraged after the assignment of the MHLW/PMDA Liaison. A meeting between the Head of the EMA's Manufacturing and Quality Compliance Section and MHLW/PMDA colleagues in Tokyo in the margin of ICH Fukuoka meeting took place in November 2010. PMDA colleagues were invited to the EMA for a specific bilateral meeting and the regular informal joint meeting of MRA partners, and also to the GMP Inspectors Working Group. Dialogue is ongoing at a technical level aiming to expand the operational scope (derestrict) of the EU-Japan MRA on GMP. To save resources most of the EU derestriction activities are planned to be conducted in conjunction with the PIC/S evaluation of Japan's planned membership.

2.7. GCP (M)

PMDA colleagues have continuously participated in a series of GCP inspectors training workshops hosted by EMA. The MHLW/PMDA Liaison Official was invited to join as a panellist the International Workshop on the draft reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in Marketing Authorisation Applications to the EMA, and provided valuable comments.

2.8. Contributions to draft guidelines and other papers

Besides the contributions described above, EMA and MHLW/PMDA regularly provide their comments to selected draft documents under preparation. For example, PMDA submitted their comments to the EMA draft guideline on the drug interaction in response to its public consultation, and EU experts from the Safety Working Party and Paediatrics Working Party provided their comments to the MHLW's draft guideline on the Nonclinical Safety Testing for Paediatric Medicines with Juvenile Animals.

3. Routine exchanges

To facilitate regular communications, MHLW/PMDA is included in the Early Notification System which is activated prior to the monthly CHMP meetings. MHLW/PMDA also receives communications under embargo following every CHMP meeting. Similarly, MHLW/PMDA provides EMA with advance information on safety measures and lists of new medicinal products to be approved. They also provide periodical safety information on pharmaceuticals and medical devices, PMDA updates and information on relevant topics and meetings taking place in Japan.

4. Ad hoc exchanges

A number of ad hoc exchanges have taken place. The majority of these exchanges were on urgent safety issues, regulatory operations and specific products including pandemic and other vaccines, and included assessment reports, guidance documents, press releases, Q&As, outcomes of the Scientific Committees on these issues and products of interest (which are translated into English when it is provided by Japan). The shared information on specific issues and products is helpful in taking prompt administrative actions by both authorities.

5. Personnel exchange, visits and meeting participations

For the last several years, PMDA have sent some of their staff members to EMA. They spent a period of circa half a year at EMA observing meetings and developing contacts with staff in their respective areas of interest.

In November 2009, the appointment of a Liaison Official from Japan was agreed between MHLW/PMDA and EMA on a pilot basis. Due to language and other considerations, EMA did not appoint a Liaison Officer to PMDA/MHLW. The placement of a Liaison Official at EMA has facilitated the development of the interactions described above. Furthermore the Liaison Official meets weekly with EMA's International Liaison Officer to discuss ongoing activities and areas that need to be progressed. These meetings are also used to coordinate responses to written requests and exchanges on specific issues of interest.

At an international awareness session, the Human Medicines Development and Evaluation Unit meeting in EMA as well as at other international meetings, the MHLW/PMDA Liaison gave an overview of Japan's regulatory system on human medicines, PMDA's International Strategy and their cooperation activities with other Asian countries.

The MHLW/PMDA Liaison Official has also participated in various Scientific Committees, conferences and workshops of EMA, other than those noted above, including CHMP, Pharmacovigilance Working Party, Patients' and Consumers' Working Party, ENCePP plenary meeting, Regulatory Science Conference, Workshop on Current Use and Future Needs of Radiopharmaceuticals Labelled with Radionuclides Produced in Reactors and Possible Alternatives and many regulatory awareness sessions. He has transmitted information obtained there to MHLW/PMDA colleagues (confidential and published information) and other Japanese stakeholder (published information only) periodically, which has been very useful in informing the Japanese public of the latest developments in the EU's human medicines regulation.

An external expert was sent by MHLW to EMA from September 2010 to March 2011 under EMA's visiting expert programme. He was embedded in the Orphan Medicines Section in EMA and provided information to EMA's Scientific Committees including COMP and the Pharmacovigilance Working Party as well as to EMA staff members.

There have been frequent MHLW/PMDA staff visits to EMA, e.g., MHLW/PMDA colleagues attended the Stem Cell therapy Workshop, GCP Workshop, Nanomedicines International Workshop and GMP Inspectors Working Group. EMA also hosted Japanese visitors at meetings with EMA staff members to discuss, for example, stem-cell based therapies, switch to OTC and Herbal medicines regulation and public pharmacovigilance communications.

Similarly, EU experts were invited to give presentations on EU's ATMP regulation at the PMDA biologics symposium. In October 2010 an informal trilateral meeting involving the Executive Director of EMA, the Deputy Commissioner of US FDA, the Councillor of MHLW and the Chief Executive of PMDA took place in Tokyo, where they addressed many policy issues of mutual interest. Furthermore, the Senior Medical Officer of EMA was invited to the 1st SRSM Annual meeting (Japan's Society for Regulatory Science of Medical Products) held in Tokyo in September 2011 to expound and discuss the role of regulatory science in developing innovative medicinal products.

6. Conclusions

In general activities in all areas intensified, especially after the Japanese Liaison Official was assigned, and there has been an overall increase in the number of ad-hoc requests for information on specific products and topics. An increasing number of staff visits and exchanges took place, with an expansion of routine involvement in the scientific work of both agencies.

The placement of the Japanese Liaison at EMA has shown to be beneficial from the perspective of education, awareness of interaction opportunities and timely communications.

The consolidation of communication and collaboration mechanisms between EMA and MHLW/PMDA continues to be an important tool in addressing public health issues related to human medicines and in increasing efforts to learn from each others' approaches as well as avoiding duplication and facilitating synergic activities.

Annex I – Statistics on EMA-MHLW/PMDA interactions

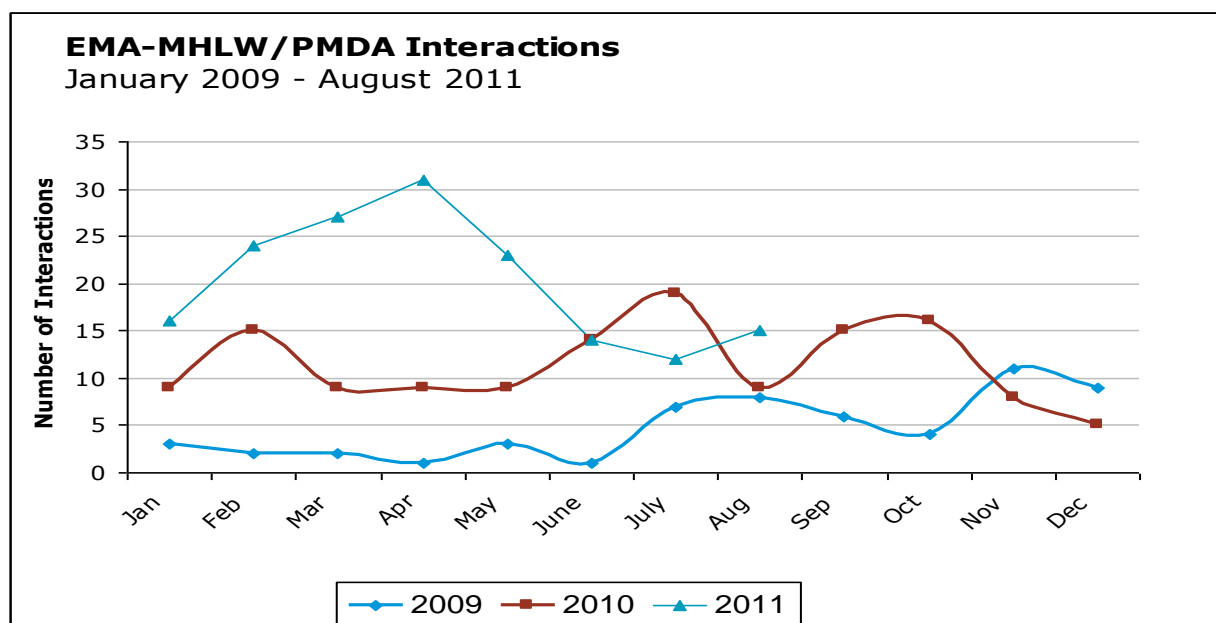


Table I – EMA-MHLW/PMDA Interactions Yearly (January 2009 to August 2011)

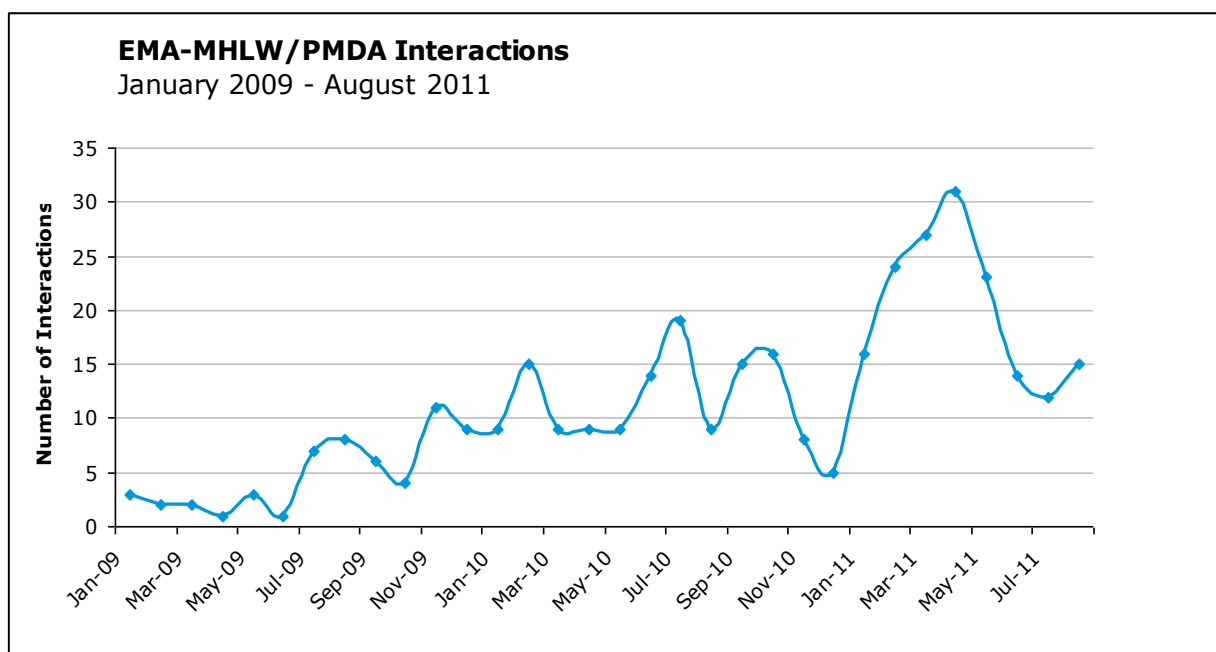


Table II - EMA-MHLW/PMDA Interactions (January 2009 to August 2011)

Annex II – Table of abbreviations used

Abbreviation	Full Text
ATMP	Advanced Therapy Medicinal Product
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
CLINAM	European Conference for Clinical Nanomedicines
COMP	Committee for Orphan Medicinal Products
EC	European Commission
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
MHLW	Ministry of Health, Labour and Welfare (Japan)
MRA	Mutual Recognition Agreement
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PSTC-NWG	Predictive Safety Testing Consortium-Nephrotoxicity Working Group
SME	Small and Medium-sized Enterprises
SRSM	Society for Regulatory Science of Medical Products (Japan)