Recommendations
of the
EU-Japan Business Round Table
to the Leaders of the European Union and Japan

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Working Party 2
Life Sciences and Biotechnologies, Healthcare and Well-being
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List of Abbreviations

Abbreviation	Meaning
ADI	Acceptable Daily Intake
ARCB	Association of Registered Certification Bodies under J-PMD Act
CBD	Convention on Biological Diversity
CE	Conformite Europeenne
ECFIN	Directorate-General for Economic and Financial Affairs of the European Commission
ECPA	European Crop Protection Association
EFPIA	European Federation of Pharmaceutical Industries and Associations
EPA	Economic Partnership Agreement
ESA	European Seed Association
EU	European Union
FQs	Fluoroquinolones
FSC	Food Safety Commission
GCP	Good Clinical Practice
GDP	Good Delivery Practice
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
HTA	Health Technology Assessment
IEC	International Electro technical Commission
ISO	International Organization for Standardization
JIS	Japanese Industrial Standards
J-PAL	Japanese Pharmaceutical Affairs Law
J-PMD Act	Japanese Pharmaceutical and Medical Device Act
JVPA	Japan Veterinary Products Association
LS & BT	Life sciences and Biotechnologies
MAFF	Ministry of Agriculture, Forestry and Fisheries
MDD	Medical Device Directive
MDR	Medical Device Regulation
MDSAP	Medical Device Single Audit Program Pilot
METI	Ministry of Economy, Trade and Industry
MHLW	Ministry of Health Labor and Welfare
MNC	Multinational Corporation
MRA	Mutual Recognition Agreement
MRL	Maximum Residue Limits
NB	Notified Body
NHI	National Health Insurance
NVAL	National Veterinary Assay Laboratory
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Co-operation Scheme
PMDA	Pharmaceutical and Medical Device Agency
PPS	Plant Protection Station
QMS	Quality Management System
RMP	Risk Management Plan
TPP	Trans Pacific Partnership
VICH	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products
WP	Working Party
WTO	World Trade Organization

Introduction

Both, Japan and the EU face numerous challenges, such as an aging population, shifting demands in almost all domestic markets and rising costs in many aspects of the welfare system, with a need to accelerate and focus on high-end innovations. This is particularly true in the areas of

- Healthcare
- Plant Protection & Biotechnology, and
- Animal Health.

The enclosed recommendations of WP-2 have the clear aim to improve the innovation capabilities of both the EU and Japan through concrete action plans in life sciences and biotechnology, focusing on measures to enhance efficient healthcare practices, food technology / supply and biotechnology.

The BRT members recognize that the EU and the Japanese governments have made some efforts on regulatory harmonization in these fields. In anticipation of post-EPA between both regions, we hope the governments will continue further actions for regulatory harmonisation and collaboration.

One asterisk (*) identifies “priority” recommendations, two asterisks (**) identify “top priority” recommendations.

Recommendations from both European and Japanese industries

General

WP-2 / # 01** / EJ to EJ Implementation of the Nagoya Protocol on Access to Genetic Resources and Benefit Sharing under coordination with industries

EU-Japan BRT members fully support the objectives of the Convention on Biological Diversity (CBD) and of the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization.

The European Parliament and the Council adopted the Regulation (EU) No 511/2014 on 16 April 2014 as a compliance measure for users under the Nagoya Protocol. Although the Regulation entered into force on 9 June 2014 and all of its provisions have been applied since 12 October 2015, there are still unclear issues regarding implementation. The BRT members call for detailed and clear guidance on the scope of the regulation under full coordination with industries.

The Japanese government is proceeding to develop domestic measures towards ratification of the Nagoya Protocol. The BRT members call for open discussion to set up a framework to implement the measures with sufficient coordination with industries.

<Yearly status report>
Some progress in our recommendation in 2015 has been seen. Namely, the requirement to make a due diligence declaration at the time of market launch in the EU for products developed outside the EU via utilizing genetic resources has been removed. The Japanese government has not ratified the Nagoya protocol and is carefully preparing domestic measures for its implementation.

<Background>
The Nagoya Protocol was adopted at the 10th Conference of the Parties to the CBD (COP10) in 2010 and went into force on October 12, 2014. It is an international agreement, which aims at sharing the benefits arising from the utilization of genetic resources in a fair and equitable way. However, it has the possibility to influence a wide range of industries, such as the pharmaceutical, plant-breeding, seeds and horticulture, animal-breeding, food and beverage, biotechnology, cosmetic, bio-control and other industries, which are utilizing genetic resources. EU-Japan BRT members are concerned that implementation of the Nagoya Protocol presents many challenges and areas of uncertainty.

We are especially concerned about the structural problem, namely the obscure scope of the Protocol based on the ambiguous definitions of some terms, such as "genetic resource" and "utilization of genetic resources". Therefore, providing countries of genetic resources may unilaterally and separately take measures for access to genetic resources and benefit-sharing. This may impose an excessive burden on the users of genetic resources, such as companies in the EU and Japan, to fulfil different access requirements in each country.

Furthermore, the users would be required to comply with the legislations of the resource providing countries, even though the contents of the legislation might be overly favourable to the provider's side. We are concerned about compliance measures for users from the EU or Japan that may impose unreasonable burden on the users of genetic resources because the terms of "research and development", related to "utilization of genetic resources", are not clearly defined in the Nagoya Protocol. This may increase the legal instability and may widely impede or delay the R&D activities of utilizing genetic resources.

In addition, we are concerned that the benefit-sharing may be required for the genetic resources accessed before entry into force of the CBD or the Nagoya Protocol, because the negotiations of Article 10 of the Nagoya Protocol are underway and there are opinions claiming that the obligation of benefit-sharing should be retroactively applied for the genetic resources which were accessed before the CBD entered into force.

The European Parliament and the Council adopted the Regulation (EU) No 511/2014 on 16 April 2014 as a compliance measure for users under the Nagoya Protocol. It entered into force on 9 June 2014 and all of its provisions have been applied since 12 October 2015. At present, each EU member state is developing domestic measures for implementation of the Regulation, and the European Commission is preparing guidance on the scope of the Regulation, as well as guidance on the utilization of genetic resources in several industry sectors.

The Japanese government has not ratified the Nagoya protocol yet and is internally preparing domestic measures for ratification and implementation of the Nagoya Protocol. EU-Japan BRT members are concerned that unreasonable financial and operational burdens may increase in relation to access to genetic resources and in implementation of the compliance measures, unless the problematic issues such as the obscure scope of the Protocol and of the compliance measures are resolved.

Furthermore, we have another concern that it may widen the gap in terms of the business competitiveness against the United States, which is not a Party of the CBD.

Healthcare

WP-2 / # 02* / EJ to EJ MRA of GMP for Pharmaceuticals

Further extension of the "Mutual Recognition Agreement" (MRA) of GMP should be proceeded in order to avoid redundant inspections of manufacturing facilities. In addition to oral dosage forms, API, Sterile and Biotechnology products are being requested to apply to the MRA. Full support is requested to expand the MRA of GMP to liquids, sterile forms and API, as well as biotech products in order to avoid redundant inspections and testing.

<Yearly Status Report>
Japan's application was approved in May 2014 and Japan officially joined PIC/S on July 1st 2014. As the guideline enforces the harmonization of the inspections among PIC/S countries, this issue might be advanced by starting negotiations between both governments.

<Background>
In March 2012, MHLW applied for PIC/S and the practical inspection by the global team was completed. However, as currently only oral solid dosage forms are included within the MRA between Japan and the EU, there are still a lot of redundant inspections of manufacturing facilities. This is not only a costly process but it also slows down the launching of new drugs in Japan, creating a significant disadvantage for Japanese patients. In order to eliminate this problem and integrate the EU and Japan economies more efficiently, harmonization of standards / guidelines and expansion of MRA should be conducted under mutual agreements. Below-mentioned are highly prioritized items for harmonization. Also, the MRA issue is one of the items of the EPA negotiation between EU and Japan.

<Other prioritized items for harmonization and MRA>
- *Safety measures from surveillance to vigilance should be harmonized with international standards.*
- *Clinical development guidelines and biological preparation standards for vaccine.*
- *Minimum requirements for biological products.*

WP-2 / # 03* / EJ to EJ <u>Mutual recognition of quality management audit results for medical devices between EU and Japan</u>

The EU and Japanese governments should establish a mutual recognition scheme for Quality Management System (QMS) audit results. In June 2015, the Japanese government announced it would officially join the Medical Device Single Audit Program Pilot (MDSAP) to share QMS audit results between United States, Canada, Australia and Brazil. improvement in efficiency and reduction of workloads for both authorities and the industry are expected. We call for a similar regulatory harmonisation approach between the EU and Japan for lower risk medical devices, e.g. those classified as Class II, ARCB under the Japanese Pharmaceutical and Medical Device Act (J-PMD Act).

As a result of the implementation of the J-PMD Act in November 2014, the ISO13485 audit report is accepted for the QMS process in Japan. However, the Japanese original requirement still remains. For a real regulatory harmonization, submission related formats / standards also need to be harmonized. We would like to request a clear direction towards a product-based and rationalized annual audit.

The EU side requests a complete harmonization by eliminating Japan's deviations on top of ISO13485. As a next step, mutual recognition of medical device products for lower risk classes should be introduced as soon as possible. Further improvements are desirable when introducing a new ISO revision. If the ISO revision differs per country (for example: ISO 60601 rev2 and rev3), the workload for manufacturers is very heavy. Therefore, the introduction schedule of new ISO standards should be harmonized, including a grace period. The EU side would also like to suggest the necessity of disseminating information on QMS ministerial ordinances in English, for the purpose of MDSAP rationalization of investigation pursuant to Chapter 3, Production and Marketing.

<Yearly Status Report>
Under the Japanese Pharmaceutical and Medical Device Act enforced in November 2014, QMS of medical devices in Japan has proceeded to be aligned to international standards. In addition, Japan announced it would join MDSAP to ensure its internationalization. Good progress has been seen for this recommendation after the J-PMD Act was implemented in November 2014.

<Background>
In June 2015, the Japanese government announced it would officially join MDSAP. MDSAP is an international cooperation programme for quality assurance of medical devices by the United States, Canada, Australia and Brazil as members, established in January 2014. Regulatory authorities of the member countries cooperatively evaluate QMS audit agencies and share audit results among member countries. Medical device companies normally have to get a QMS audit in each country. However, under MDSAP a single QMS audit results will be valid among member countries. This programme will reduce the burdens on both companies and authorities. Although there are issues to be solved to implement this programme, distribution of medical devices will be stimulated between the member countries of MDSAP. Similar scheme between the EU and Japan should be considered.

Based on the Medical Devices Directive (MDD) of the EU and the J-PMD Act, QMS audit results are required for each application for a license to introduce new medical devices into the market. In Europe, the regular annual ISO audit results can be used for all applications during the period in which the ISO audit is valid. Although Japan has started to accept QMS audit results at a specific manufacturing site for products with the same generic name under certain conditions, a number of RCBs still require submitting QMS audit results for each application. Further alignment is necessary.

WP-2 / # 04* / EJ to EJ <u>Mutual recognition of medical devices product licenses</u>

Mutual recognition of medical device product licenses between the EU and Japan should be introduced. Regulations of low risk class II devices are similar in the EU and Japan. Therefore, mutual recognition of this category of products may be realized earlier. After a basic agreement on the Trans Pacific Partnership (TPP), the Japanese government is revising the law proceeding convergence of approval conditions of medical devices. A similar approach is needed between the EU and Japan. PMDA and MHLW should introduce mutual recognition of medical device product licenses with low risk of class II devices by taking the difference of classification of medical devices between Japan and the EU into account. By harmonizing QMS and classification it should be possible to introduce new products within the same time frame and in one process. It is desirable that this issue is solved quickly.

The EU will pursue MDR, but not enough information is communicated to Japan. We would like to suggest that the EU communicates with the Japanese government about the new MDR implementation.

<Yearly Status Report>
No progress / no dialogue has been seen. However, there have been some improvements through the implementation of the Pharmaceutical and Medical Device Act, which makes Japan accept the audit report ISO13485 issued by the countries. The PMDA's performance has been improved to shorten approval times for medical devices. ISO14155 has been accepted but we request further improvement.
Based on the Pharmaceutical and Medical Device Act, some Class II and Class III products will move to "Ninsho" application. As a result, there has been no progress on "mutual recognition" discussions, but improvement on the speed of approvals for medical devices has been seen.

<Background>
Mutual recognition of licenses for medical devices in Japan and the EU would make it possible to introduce new products in both the Japanese and European markets within the same timeframe and with one process.

The Japanese government is preparing the amendment of the Pharmaceutical and Medical Device Act in response to the TTP agreement. The proposed amendment says companies in TTP countries can use certified Notified Bodies in any TTP country in order to obtain Ninsho approval, which will be valid to distribute approved Medical Devices in Japan. This can be one step for mutual recognition but it would negatively impact on the distribution of Medical Devices between the EU and Japan.

As mentioned before, it could be possible to start with lower risk devices.

The evaluation scheme between the Medical Devices Directive of the EU and J-PMD Act are quite similar, with

- Evaluation schemes based on registered 3rd party bodies (Notified Bodies)
- Essentially quite similar requirements
- Based on ISO/IEC or JIS standard compliance

With these similarities, mutual recognition should be easy to implement.

WP-2 / # 05* / EJ to EJ <u>Mutual recognition of clinical trial results for medical devices</u>

Mutual recognition of clinical trial results for the development of new medical devices should be accelerated. At present, the standards of clinical trials in the United States, EU and Japan are seen to be almost equivalent and there are several cases where clinical trial results are mutually recognized between EU and Japan. EU Japan BRT members request to both governments in the EU and Japan to accelerate mutual recognition of clinical trial results by increasing such cases and showing clinical trial conductors implementing guidelines.

Introduce a mutual recognition of clinical trial results for medical device development. Foreign clinical trial data have been accepted as a part of the application dossier when: i) standards for conducting medical device clinical trials are set by the regulations of the country or region where the trial was performed, ii) the standards are equivalent or surpass the Japanese medical device GCP, and iii) the clinical trial was conducted in accordance with the standards or considered to have equivalent

level of quality. The Japanese government encourages active use of consultation service on individual medical device applications in advance provided by the Pharmaceuticals and Medical Devices Agency (PMDA) to address the use of foreign clinical trial data for the application of a device.

At present, clinical data are often accepted because the standards of clinical trials in the United States or the EU are seen to be equivalent or sometimes more sophisticated than those required by the Japanese medical device GCP. However, then additional data are required with unclear reasons.

Japan GCP (J-GCP) has been harmonized with ISO14155, but the EU side requests Japan to improve the actual operation of J-GCP. The clinical trials performed in EU countries according to ISO 14155 should be easily accepted and if not accepted, an explanation with a scientific background is a must. In addition, the Japanese government should prepare a clear definition for accepting/preparing clinical trial reports.

While the harmonization between GCP and ISO14155 for medical devices in Japan has made progress, we hope for early disclosure of a clear guidance for judgment on the need for clinical studies, conditions for acceptance, etc. in order to make the actual operation of GCP smoother. Regarding the guidance for the preparation of the Clinical Evaluation Report, we request the Japanese Government to issue the guidance as early as possible.

We expect that the standard for deciding whether clinical trials are necessary or not will be clearly established. The Government should publish guidelines for creating clinical evaluation reports as soon as possible.

<Yearly Status Report>
A certain level of progress has been seen for this recommendation. We expect that the Japanese Government will publish guidelines for creating clinical evaluation reports as soon as possible.

<Background>
For the new medical device applications in Japan, the clinical trial results acquired in the EU could not be accepted so far. However, several cases can be seen where the Japanese medical device companies submit new medical device applications with clinical trial results in the EU and obtain regulatory approval in Japan. Also, there are some cases reported where the clinical trial results acquired in Japan are applied to the new medical device applications in the EU. However, environmental improvement such as showing regulatory authorities in the EU and Japan an implementing guideline in order to lessen the burden of development costs and to ensure patient access to the innovative new medical devices is very limited today.

With regards to the procedure between the United States and Japan, mutual recognition of clinical trial results is already being practiced under the clinical trials by comprehensive and simultaneous processes, such as "Harmonization By Doing (HBD)" by both regulatory authorities in the United States and Japan.

Differences in the definition of GCP between Japan and the EU currently prevents the use of non-Japanese clinical trial results in the application for new medical devices in Japan. Mutual recognition of clinical trial results would make it possible to make new products available to patients in Japan and the EU within the same timeframe and through one process, ensuring a high level of quality while reducing the burden on manufacturers. Early disclosure of clinical trial-related guidance will promote the entry of overseas companies to the Japanese market.

Plant Protection & Biotechnology

WP-2 / # 06* / EJ to EJ Shortening review times of plant protection & biotechnology products

Shorten review times for authorization to place novel plant protection products in the market and approval of importation of commodities treated with novel plant protection products and/or derived from biotechnology by the harmonization of safety dossier and risk assessment as well as streamlining the review process.

Possible area for improvement to shorten times might be:

- Further harmonization of the dossier on human safety and acceptance of summaries in English.
- Opportunistic use of the evaluation results from foreign countries in order to reduce the resource burden in authorities.
- MAFF, MHLW and FSC should start harmonization to shorten review times. Realization of parallel review for human dietary risk assessment within competent authorities, which is currently undertaken in a sequential manner, MAFF => MHLW => FSC => MHLW => MAFF.
- Association and synchronization of review for domestic registration with that for import MRLs.

<Yearly Status Report>
Some progress has been seen in the introduction and harmonization of safety dossiers (J-MAFF) and in the revision on the application timing for import MRLs (J-MHLW).

<Background>
Delivering novel and safe plant protection products and seeds has utmost importance for the plant protection & biotechnology companies in order to meet the needs of the growing world population requiring high quality foods and feeds. While R&D-intensive companies are continuously and heavily investing in research & development of technologies, the innovation will not contribute to the food production without governmental approval. Therefore, early market access of novel plant protection products is crucially important not only for R&D companies but also for farmers who have to be competitive on their agricultural production, as well as consumers whose living is dependent on the sustainability of food production. The delay of market access of novel products will cause technology gaps resulting in unnecessary disadvantage to farmers due to the limited access to innovative products which are safer and more effective. In addition, the delay of review for import approval on agricultural commodities, including the establishment of import MRLs, may limit the

access to innovative technology in exporting markets due to trade barriers in the importing countries.

Though Japanese ministries have taken measures to shorten review times of human safety studies of plant protection products and some further measures like the harmonization of dossier format for registration application with the OECD dossier format (J-MAFF) and the revision of the guideline for import tolerance application (J-MHLW), the time-to-approval is still lagging behind other countries, e.g. the US and Canada. This kind of technology gap should be avoided to give competitiveness in food production.

WP-2 / # 07* / EJ to EJ <u>Acceleration and dissemination of scientific knowledge on GMOs by both the governments and the private sector</u>

The governments and the private sector should implement concrete actions in order to increase public awareness and societal acceptance on the benefit and contribution of Plant Protection & Biotechnology to the sustainable supply of safety foods.

To achieve these objectives the Japanese and European biotechnology and bio-industry associations should work closely with other sectorial organisations and their respective authorities.

<Yearly Status Report>
No progress has been seen for this recommendation.

<Background>
While plant protection and biotechnology significantly contribute to the sustainable food production for an ever growing population, the contribution of new technologies has never been well recognized. Moreover, the benefit of improved quality traits on imported seeds has not been fully addressed. Considering the possible limitation of future access on foods and feeds as a consequence of limited arable land and global competition on limited foods, new technologies bringing higher productivity are required.

It is necessary to increase the societal acceptance of GMO as an option to increase and sustain the agricultural productivity in the world through awareness-building on the benefit of this technology to better life.

<u>Animal Health</u>

WP-2 / # 08* / EJ to EJ <u>Mutual recognition of GMP and marketing authorization for animal health products</u>

With regard to the mutual recognition of European and Japanese marketing authorizations and recognition of GMP certification for veterinary products, MAFF and the European agency should accept GMP certification of the other party where the GMP requirements are similar or equivalent.

<Yearly Status Report>
MAFF revised regulations to issue accreditation licenses written in both Japanese and English on 25 December 2014. This change accommodated a request from JVPA. However, there is no example of mutual recognition at product level as of December 2015.

<Background>
Overseas production facilities that are involved in manufacturing veterinary medicinal products imported into Japan have to be accredited by MAFF even though their GMP status is authorized by European authorities. This process involves a large amount of administrative work. An EU-Japan Economic Partnership Agreement should aim for mutual recognition of European and Japanese marketing authorization for veterinary products by starting off with mutual recognition of GMP certification of veterinary medicines where the GMP requirements are similar or equivalent.

Healthcare

WP-2 / # 09** / EJ to E Evaluation of innovation values for pharmaceuticals in prices

The EU government should reinforce its innovation policy to member states and clarify its healthcare policy, resulting in the appropriate evaluation of the value of pharmaceuticals. If member states introduce healthcare technology assessment (HTA) for their reimbursement system, they should carefully adapt appropriate methods and processes so as not to impede patient access to new pharmaceuticals and discourage innovations.

<Yearly Status Report>
No progress has been seen for this recommendation. The Directorate-General for Economic and Financial Affairs of the European Commission (ECFIN) issued a report on drug cost containment methods of member states and recommended an "EU reference price". Several member states have introduced HTA evaluation in their reimbursement systems. We would suggest following a reimbursement pricing system which clearly recognizes innovation and innovative new products.

<Background>
In the EU, innovation policy is stated by the Lisbon declaration and the G10 group report indicating the importance of innovation in pharmaceuticals. However, each state operates its own healthcare system in different ways, resulting in gaps in survival rates and the QOL of citizens. Under the current economic condition, prices of pharmaceutical products are targeted as a major tool for medical cost containment. BRT members call on the EU to clarify their healthcare policies and discuss the total improvement of healthcare situations in member states by securing appropriate healthcare budgets, preventing interference with patient access to new medicines, and considering the proper utilization of healthcare technology assessment.

Animal Health

WP-2 / # 10* / EJ to E Introduction of "1-1-1 concept" for all animal health products

Introduce 1-1-1 concept for all products (one dossier – one assessment – one decision on marketing authorization applicable to all EU countries). A concept should be worked out between the respective governments/authorities.

<Yearly Status Report>
Some progress has been seen for this recommendation, although there is no example at product level as of December 2015.

<Background>
One of the key objectives of the European Union is to create a single market for goods. This goal has yet to be achieved in the animal health industry with the exception of centrally authorized products. In line with the concepts already existing in the EU (i.e. quality, safety and efficacy described in one single EU dossier as the basis for granting marketing authorizations for veterinary medicinal products, one single assessment of the dossier employing the best expertise, resulting in one decision for marketing authorization) the animal health industry in Europe is seeking a systemic change based on the one, one, one concept ("1-1-1 Concept") for all products. This appears to be the most simple and straightforward way to address all of the major shortcomings of the current system and to finally achieve the goal of a single market for safe and efficacious veterinary medicines.

Plant Protection & Biotechnology

WP-2 / # 11* / EJ to E Maintenance of Import MRLs into the EU to allow free trade of food commodities

Securing international trade of safety foods avoiding excessive protection measures for food safety.

<Yearly Status Report>
This is a new recommendation.

<Background>
The EU should maintain sound scientific risk assessment for the Import MRLs as stipulated in the REGULATION (EC) NO 396/2005, while the REGULATION (EC) NO 1107/2009 governing plant protection products and the active substances contained in those products in the EU, may prohibit introducing certain substances, which are deemed hazardous based cut-off criteria into the European market.
In the absence of necessary Import MRLs, the food commodities containing the residue of the active substance is prohibited for importation even though the said substance is approved in the exporting countries and the residue does not cause any harmful effect on the human health.

Healthcare

WP-2 / # 12** / EJ to J The revision of the rules for the pricing and prescription of innovative new drugs

1. Full-fledged implementation of the new drug pricing system

The premium for new drug creation and elimination of unapproved / off-label use drugs will be continued until March 2018. This is welcome as it supports incentives for innovative drug development, however, it is only the continuation of a trial scheme. The Japanese government should finalize the implementation of the new, internationally competitive drug pricing system in Japan based on the industry proposal, since in addition to innovation rewards it is also protecting public health. Furthermore, it adds an element of predictability and stability so that the industry can adequately plan, forecast product requirements and effectively manages inventory as well as the distribution of products across Japan.

<Yearly Status Report>
Although the "new" drug pricing system will be continued until March 2018, it is only the continuation of a trial scheme. No practical progress has been seen for this recommendation.

<Background>
The National Health Insurance (NHI) price reform proposed by the industry has been positively reviewed by the Central Social Insurance Medical Council (Chuikyo) in December 2009 and the government decided to start a pilot implementation in April 2010. This represented a significant improvement, as it provides price stability for innovative drugs and was seen as a positive signal that the Japanese government is willing to reward innovation in the medical field. The premium for new drugs will be continued until 2018. As a compensation for this new scheme, the government will attach a system that fosters the registration of "unapproved/off-label use drugs". Companies have received requests on development of many unapproved/off-label use drugs and proceeded with those constructively. Furthermore, on several occasions companies have received additional requests on development of hundreds more unapproved/off label use drugs.

However, in the FY2016 drug pricing system reform, Chuikyo concluded to postpone full-fledged implementation of the premium for new drug creation to FY2018 revision, even though the industry strongly requested this. The conclusion brings the industry deep concerns about sustainability for evaluation of innovations. The Japanese government should implement the new premium system for innovative new drugs at the FY2018 drug pricing system revision to evaluate the companies' efforts for elimination of the so-called drug lag in Japan and research and development of innovative new drugs.

2. Abolition of the market expansion re-pricing

The re-pricing system rule by market expansion can adversely affect innovation in Japan and therefore, should be abolished.

<Yearly Status Report>
The situation has deteriorated, with a proposed revision of the re-pricing rule targeting "huge selling" drugs with price cuts of up to 50%.

<Background>
The abolition of the market expansion re-pricing was not accepted by Chuikyo even though industries strongly requested the elimination of the system. While the agenda for the 2016 NHI pricing discussion between Chuikyo and the industry included topics such as "NHI pricing for long-listed products" and "continuation vs. discontinuation of incentives for innovative drug development", it did not include "abolition of market expansion re-pricing". Furthermore, the government additionally introduced a new extra (huge sales) market expansion re-pricing at FY2016 revision. Therefore, we urge to discuss this topic to abolish both re-pricing rules by market expansion in the next pricing system reform in 2018, which is contrary to the policy of evaluating pharmaceutical innovation.

3. Abolition of the 14-day prescription rule

EU-Japan BRT members call on the Japanese government to abolish the 14-day prescription rule for all new drugs in line with the recommendation of the government's Regulatory Reform Council in 2015.

<Yearly Status Repot>
No major progress has been seen for this recommendation.

<Background>
Despite the government's policies to promote new drug development, patient access to innovative drugs is hindered by the 14-day prescription rule, which restricts the prescription length to a maximum of 14 days for all new drugs in the first year after their launch. This practically means a delay of one year in patient access to drugs which are already in extensive use abroad. The safety of new drugs in Japan is now underpinned by the post-marketing surveillance system, and by the introduction of a Risk Management Plan (RMP) in 2013. Accordingly, EU-Japan BRT members call on the Japanese government to revise the prescription length for all new drugs.

4. Sufficient discussion with stakeholders on introduction of HTA for drug pricing

EU-Japan BRT members urge the Japanese government to sufficiently discuss with all stakeholders the introduction of HTA for the drug pricing system in Japan.

<Yearly Status Report>
No major progress has been seen for this recommendation.

<Background>
The methods of HTA for drugs and medical devices have been discussed in Chuikyo. The government decided implementation of HTA evaluation for certain approved products as a trial basis since April 2016. And also Chuikyo intends to ask companies to submit HTA results on new drugs at the time of reimbursement price applications in future. We strongly ask the Japanese government to sufficiently

discuss the process of making appropriate framework with the industry, academia, patients and all stakeholders. We have seen that some countries have caused the limited patients access to innovative new drugs.
Furthermore, HTA may hinder the companies' willingness to conduct research and development activities for the innovative new drugs in the country. The Japanese government should consider these possible risks and discuss with all stakeholders so that HTA may not hinder the patient access to the innovative treatments and the improvement of public health.

5. Maintain biennial drug price revision and appropriately reflect the increase of consumption tax ratio into the NHI prices

A) Maintain biennial price revision
EU and Japan BRT members strongly believe that the R&D-based pharmaceutical industry is a leading industry of the Japanese economy. From the viewpoint of Japan being an innovation leader, annual NHI price revision for pharmaceutical and medical device products would be inconsistent with the government's growth strategy, and would damage the companies' competitiveness. EU and Japan BRT members strongly request to the Japanese government that comprehensive discussions, including the viewpoint of evaluation and support for new drug discovery and further growth of the industry should be initiated.

B) Reflect appropriately the increase of consumption tax into the price
Also, following the medical service fee revision in 2016, there will be an irregular price revision for pharmaceuticals in April 2017 due to increase of the consumption tax ratio in Japan. This price revision in April 2017 should not be based on the actual market price from a price survey, but only on the increase of the consumption tax ratio. That is, adding a certain percentage on to the reimbursement prices, which is the same procedure as in the price revision in 1989, is the preferable option.

<Yearly Status Report>
This is a new recommendation.

<Background>
The R&D-based pharmaceutical industry is anticipated to contribute to the growth of the Japanese economy as an innovation leader. Several promotion policies, focusing on the development of the pharmaceutical industry are included in the "Japan Revitalization Strategy" and "Healthcare Policy" documents, announced by the government last year. On the other hand, the new introduction of annual price revisions for pharmaceutical products and medical devices as a medical expenditure containment policy have been discussed in the government's councils, such as the Council on Economic and Fiscal Policy, chaired by the Prime Minister of Japan.

Current rules for NHI price revision are developed with biennial medical service fee revision. Therefore, it is highly inappropriate to discuss only the "frequency" of the price revision for only pharmaceutical and medical device products, without consideration about consistency with medical service fee or other NHI pricing rules. Significant difficulty in annual price revision is anticipated due to the following reasons, i) market price survey for drugs is not feasible in such a short period, ii) the accuracy is not secured if the market price survey is conducted in a short period, and iii) annual price revision hinder companies' incentive for the investment in innovative

products. Also, from the distribution point of view, significant disorders will occur in the market such as re-writing price data in the system of hospitals or wholesalers due to annual price revision for pharmaceutical and medical device products. EU and Japan BRT members have concerns that this unbalanced medical expenditure containment policy by the Japanese government could damage industry's competitiveness and growth capability.

As for the consumption tax ratio, it will be raised in April 2017. From the viewpoint that this price revision is clearly different from the regular biennial price revision, the price revision in April 2017 should not be based on the actual market price from a price survey, but on only the increase of the consumption tax ratio.

WP-2 / # 13 / EJ to J <u>Appropriate assessment of innovative values of medical devices in prices</u>**

1. Sub-dividing the current functional classification

Promote sub-dividing of the current functional classification in the special treatment material system in order to accelerate appropriate evaluation of the innovativeness.

<Yearly Status Report>
No major progress has been seen in 2015 for this recommendation.

<Background>
Different from pharmaceutical product-oriented pricing systems, about 280,000 medical devices are classified into about 900 functional classes in Japan and one reimbursement price is set for one functional class based on structure, intended use, effectiveness and so on.

Currently, various products, having various market prices, have the same reimbursement price within one functional class. For the revision of reimbursement prices the price reduction of old products influences the reimbursement price of new products. In order to realize the appropriate evaluation of the innovativeness in medical devices, the reimbursement price of new products should be set separately from the price of old product. It is desired that the reimbursement pricing system should be revised closer to a product-oriented system.

2. Careful introduction of HTA based on characteristics of medical devices

EU and Japan BRT members request both governments in EU and Japan to examine carefully the appropriate HTA system design by considering the factors:

i) QALY, a sort of HTA evaluation index for pharmaceutical products, cannot be applied for evaluation about medical devices

ii) users' skills and techniques of each medical device must affect the evaluation and

iii) medical devices have a shorter improvement cycle.

In addition, we ask both governments for their consideration in order not to hinder the creation of innovative products nor delay the listing to the medical insurance reimbursement and not to impose an excess burden on the industry for developments of databases or human resources for HTA.

<Yearly Status Report>
This is a new recommendation.

<Background>
Following several EU member states, the Japanese government determined to introduce HTA into approval processes for the medical insurance reimbursement of medical devices on a trial basis at the medical service fee revision in 2016. QALY cannot be applied to the evaluation of medical devices, which is different to pharmaceutical products as the users' skills and techniques significantly influence the outcome of the treatment. Similar issues can be seen in the EU where HTA procedures are already introduced prior to Japan. Considering this, both governments in the EU and Japan should carefully examine an appropriate HTA system design by considering such special characteristics for medical devices.

Furthermore, both governments in the EU and Japan should be careful about HTA not to hinder innovative quality improvements in medicine and patient access to cutting-edge medical technologies.

3. Abolishment of the foreign price reference system in Japan

The foreign price reference system in Japan should be abolished because the average price in Japan is already only 80% of foreign prices according to MHLW documents and the upper limit of the price variance between foreign countries and Japan no longer makes sense in reality.

<Yearly Status Report>
At the medical service fee revision in 2016, the government determined to lower the upper limit of reimbursement price variance between foreign countries and Japan from the current level 1.5 times to 1.3 times.

<Background>
As one of a series of medical expenditure containment policies, at the medical service fee revision in 2016 the Japanese government determined to lower the upper limit of reimbursement price variance between foreign countries and Japan to 1.3 times so that the shrinkage of the price variance of medical devices can be achieved. It is required that the reimbursement pricing system should be revised by considering the special characteristics in Japan, such as the necessity to support wholesalers' distribution costs (a very important role was played by wholesalers when disaster hit Japan) and medical institutions because the patients are decentralized in Japan.

4. Maintain biennial price revision

EU and Japan BRT members strongly oppose yearly revisions of reimbursement prices and support maintenance of the current biennial revision scheme.

<Yearly Status Report>
New recommendation

<Background>
Same as the recommendation #12-5

Recommendations from European industry

Animal Health

WP-2 / # 14* / E to EJ Prudent use of antibiotics in animal health

The establishment of a cascading system prioritizing use of approved drugs and formulations where they exist, rather than other available products lacking such claims, would promote responsible use of all drugs in animal health.

<Yearly Status Report>
MAFF continues to promote prudent use of antibiotics in animal health.

<Background>
In common with the rest of the world, Europeans and Japanese are concerned by the development of resistance to antibiotic medicines used in human health and the potential threat that the use of antibiotics in animal health will accelerate this process. The use of antibiotics as growth promoters has been prohibited in the EU since 2006. As a responsible industry, the animal health industry seeks to work with veterinarians, farmers and the feed industry to dispel the myths about the use of antibiotics in animals and promote their responsible use.

MAFF requested Marketing Authorization Holders of fluoroquinolones, 3rd and 4th generation of Cephems, 15-membered ring macrolide to indicate the "2nd choice drug" on their packages and to specify precautions such as "Veterinarians should change a medication based on their judgment about the efficacy of the drug within 3 days after the initial administration" on the labelling of products for food animals in November 2014.

WP-2 / # 15* / E to J Regulatory harmonization for animal health products

The food animal product registration process is particularly cumbersome, involving a sequential review by MAFF followed by the FSC and the MHLW. Decision criteria and timelines for the following stages of the review process are not provided, resulting in extended review times.

In 2014, MAFF held a series of explanatory meetings to update the J-PMD Act and their approaches for shortening the review time for animal health products. It is recognized that MAFF, FSC and MHLW started discussions on how to shorten review times for livestock products (i.e. introduction of parallel deliberation among the authorities.) Discussions among the authorities are ongoing.

<Yearly Status Report>
MAFF did a tremendous job to align the Japanese regulations with that of the EU by shortening the withdrawal period following the administration of oil adjuvant vaccines.

<Background>
Restrictions on the withdrawal period for innovative oil-adjuvant vaccines are especially stringent in Japan. Implementing a scientific health risk assessment approach in establishing the withdrawal period and the increased collaboration of different ministries involved in food safety would certainly improve the access of animals and animal owners to innovative animal health products which are readily available in Europe. While such global new veterinary medicinal products already go through rigorous review processes in Europe and the USA prior to registration, it requires substantial additional testing in J-PMD Act before an approval is granted.

An additional important aspect is the negative impact on animal welfare: since the regulatory requirements are not harmonized, the companies are required to repeat some tests on animals in Japan even though results of identical tests are already available and are fully compliant with stringent frameworks like GLP or VICH. Recognition of animal welfare aspects is not yet optimal in the administration of animal health products in Japan. Japan should minimize the use of animals by accepting more overseas data and alternative approach.

WP-2 / # 16* / E to J <u>Shortening review times for animal health products</u>

Shorten review times for new product applications for food animals. MAFF, MHLW and FSC should start harmonization to shorten review times. The process is complicated in addition to a review period that already for pet animal products (not requiring Acceptable Daily Intake (ADI) and Maximum Residue Limits (MRL)) is among the longest in the world. A lot of questions are asked in the process that might be academically interesting but are not necessarily safety- or efficacy-related. Clarifying registration requirements and shortening review times for the import of recombinant vaccines from Europe should also be implemented.

<Yearly Status Report>
Significant progress was made by MAFF. They explained to the industry in August 2015 that a new review process will be introduced to shorten the overall review period for veterinary medicinal products for food-producing animals by allowing MAFF, MHLW and FSC to review in parallel in the near future.

<Background>
In Japan, marketing authorization of a veterinary medicinal product is granted by MAFF. For an animal drug intended for use in food-producing animals, FSC and MHLW are also involved in establishing the acceptable daily intake and maximum residue limit respectively. The review process, involving three different authorities, is rather complex and certainly has some room for efficiency improvement. Also, the review can take an extremely long time until completion. Hence, it delays the access of animal owners and animals to innovative animal health products. This is also true with the introduction of recombinant vaccines from Europe due to lengthy processes

of implementing the Cartagena protocol even if the vaccine has already been extensively used in Europe.

Healthcare

WP-2 / # 17* / E to J Application of GMP on medicinal gases (manufacture of medicinal gases) in Japan

Reinforce the regulation for GMP on medicinal gases in Japan. MHLW has started these initiatives along with industries. But industries are protective to non-GMP facilities because of financial implications.

<Yearly Status Report>
Some progress has been seen for this recommendation. In February 2012, MHLW notified medical gas suppliers that they should voluntarily obey the industry standard. This standard, called the JIMGA standard, was almost compatible to GMP standard but a little looser. PMDA/MHLW reinforced the GMP for medicinal gases through the PIC/S. Japan officially joined in July 2014. MHLW has announced the GMP standard only to the JIMGA core team, which is an updated JIMGA standard and almost equivalent to PIC/S Annex 6. The formal announcement will be made in a couple of months.

<Background>
Medicinal gases are drugs or medicinal devices and have to be compliant with governmental regulations. The main regulations are the national Pharmacopeia, GMP (Good Manufacturing Practices) and GDP (Good Delivery Practice). Annex 6 describes GMP and GDP for production and distribution of medical gases. The currently loose interpretation of GMP in Japan, along with relatively low standards of the Japanese Pharmacopeia, is at a lower level compared to those applicable in Europe or the US. We would like to suggest a reinforcement of regulations on GMP for medical gases in Japan.

WP-2 / # 18* / E to J Requirement of Japanese version of the clinical trial protocol and investigators brochure

The Japanese health authority requires a clinical trial protocol and investigator's brochure in Japanese. Translation from English is required for clinical trial notification in Japan. The acceptance of English-only materials for global clinical trials performed in Japan requires further English language education of Japanese regulators. However, if applications could be made in English-only, it would substantially accelerate the process and make innovative drugs earlier available to patients in Japan.

<Yearly Status Report>
No progress has been seen for this recommendation but currently, an English application format is being positively discussed.

<Background>
The Japanese health authority requires a clinical trial protocol and investigator's brochure in Japanese. Translation from the original English version is required for clinical trial notification of global trials in Japan. Therefore, the requirement is considered to be a cause of delay to the start of patients' enrolment in Japan.

WP-2 / # 19* / E to J <u>Shorten or eliminate national tests for vaccines</u>

For imported vaccines, national tests in Japan and manufacturing sites have been conducted (for more than 20 years in some instances). National tests for vaccines should be eliminated or reduced to an absolute minimum.

<Yearly Status Report>
Some progress has been seen for this recommendation.

<Background>
Vaccine production is conducted according to GMP and PMDA periodical audits of production sites. However, the higher quality assurance of vaccines is strongly demanded by society. The GMP of manufacturing countries should be accepted by the Japanese authority and the national tests for vaccines in Japan should be eliminated or reduced to an absolute minimum.