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

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Working Party B
Life Sciences and Biotechnologies, Healthcare and Well-being
(Final Version)

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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
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
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 are facing 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 particularly in the areas of

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

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

The BRT members have seen that the EU and the Japanese governments 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 collaborations.

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

Recommendations from both European and Japanese industries

General

WP-B / # 01** / EJ to EJ Sensitive handling of approval / adaption of CBD / the Nagoya Protocol on Access to Genetic Resources and Benefit Sharing

The EU government has already ratified the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their utilization to the Convention on Biological Diversity. EU-J BRT members strongly call for the re-examination of several issues in the regulation (EU) No. 511/2014 and/or the Implementing Acts draft, as these will become serious impediments to the business operations including international trade of a wide range of products and activities for research and developments. In particular, the requirement to provide a due diligence declaration at the time of market launch in the EU for products developed or manufactured outside of the EU and utilizing genetic resources must be removed.

The Japanese government should not ratify the Nagoya Protocol until (1) the sufficient encouragement for denial of the retroactive application to genetic resource is made, (2) the benefit sharing scheme of the genetic resources is determined that it will not be applicable for the genetic resources, which companies and institutes have already held, (3) utilization stage is reached where it can be determined that the retroactive application to genetic resource utilization will be denied for Japan, and (4) the appearance of clear feasible measures, which could be implemented by utilizers of genetic resources such as companies and research institutions without unreasonable costs. Furthermore, when discussions are held on feasible measures toward ratification of the Protocol, the Japanese government must not proceed in a hasty manner, but reach a conclusion only after conducting sufficient coordination with the industry.

<Yearly status report>
New recommendation

<Background>
The Nagoya Protocol, annexed to the Convention of Biological Diversity (CBD), went into effect on October 12, 2014. The Nagoya Protocol is a multilateral arrangement, in which the economic scheme for benefit sharing between providers and utilizers of genetic resources is defined, and it possibly influences the widely-related industries such as the food manufacturers, the forestry, the pharmaceutical, the seeds, the cosmetics, the bio fuel and others, which are utilizing genetic resources. However, the Nagoya Protocol had been adopted at the 10th Conference of the parties of CBD (COP10) in 2010 without sufficient coordination with the industries.
EU-Japan BRT members are especially concerned about the structural problem, of which the genetic-resource-providing countries may unilaterally legislate the obligations of the resource utilizing countries in accordance with the Provision 1 of

Article 15 in the Nagoya Protocol. This structure may also impose the utilizers such as companies in the EU and Japan to obligate for compliance of the legislations of the resource providing countries, even though the contents of the legislation is favourable to the provider's side. Besides, we have another concern that the unreasonable burden for monitoring the proper usage of the genetic resources may be imposed for utilizing companies.

In addition, it is also a risk that the time of acquisition of the resources may be retroactively determined to the time before the effect of the CBD or the Nagoya Protocol, because (1) there are opinions claiming that the time of acquisition of the genetic resources should be retroactively applied for the period after which the CBD was enacted, or (2) negotiations are underway so that the genetic resources which were utilized in the past should be in the scope of the benefit sharing

Furthermore, considerations with research and development (R&D) activities are not sufficiently defined in the Nagoya Protocol. This may increase the legal instability and the risk to widely hinder or delay the applications of the innovative outcomes from R&D activities utilizing genetic resources, unless the clearer position of each country concerned with regard to the scheme of the benefit sharing is developed.

On the other hand, the EU government has already adopted the Nagoya Protocol. The Regulation (EU) No 511/2014 of the European Parliament and the European Council (adopted in March 2014 and April 2014, respectively, became effective as of June 9, 2014) defines the intraregional procedures with regard to the Nagoya Protocol. The EU government has drafted the Implementing Act and they are preparing for the finalization within the first half of 2015 followed by the effect as of October 2015. The industries have concern about the specific contents, such as "Due diligence declaration at the stage of the final development of a product" in the Article 7, which may cause significant barriers to the business operations. Different industry sectors including the European Crop Protection Association (ECPA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Seed Association (ESA) and Europa BIO submitted comments to the EU Commission on 9th of Jan. 2015 addressing issues and areas of uncertainty associated with the Regulation and the Implementing Acts. With regards to the particular concern on the requirement for due diligence declaration for the products developed outside of the EU, it's addressed in the ECPA letter to the Commission "ECPA believes that no declaration should be made where the utilization has taken place outside of the Union. There is no legal basis in these paragraphs to extend the geographical scope of the basic Regulation and such a broad geographical raises questions as to compliance with WTO rules."

For the companies in both EU and Japan, it is expected that the financial and operational burdens to access to the genetic resources in the outside of the region or country may increase whereas business predictability may be limited by adoption of the implementing measures from the Nagoya Protocol, unless these many problematic issues such as unclear scope of the rules are resolved. Furthermore, there is another concern that it may widen the gap in terms of the business competitiveness against the United States, which is not a member of the CBD.

Healthcare

WP-B / # 02* / EJ to EJ MRA of GMP for pharmaceuticals

Further extension of "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 Bio products are being requested to apply to the MRA. Full support is requested to expand the MRA of GMP to liquids, and sterile forms, API and bio products 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 EU-Japan economics 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 guideline and biological preparation standards for vaccine.*
- *Minimum requirements for biological products.*

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

Improve mutual recognition of Quality Management System (QMS) audit results for lower risk medical devices, e.g. those classified as Class II, ARCB under the Japanese Pharmaceutical and Medical Device Act (J-PMD Act).

All industry-related manufacturers request PMDA and MHLW to further harmonize and streamline the QMS audit results. MHLW has notified that RCBs can accept non-Japanese QMS audit results. However, ISO13485 continues to be only one part of the Japanese QMS ministerial ordinance. In addition, the recognition system of "Application for Accreditation of Foreign Manufacturers" should be considered. Even if QMS is evaluated on ISO13485, all industry-related manufacturers have to be registered and are obliged to stick to the additional Japanese requirements.

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 are also to be harmonized. Therefore, 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 grace period.

About the cost of QMS audit, there is a test calculation that the cost will increase depending on the number of medical devices under the same "State of conformity". We request to review the price of QMS audit after a certain period.

<Yearly Status Report>

Good progress has been seen for this recommendation with the acceptance of ISO 13485.

<Background>

Based on Medical Devices Directive (MDD) of the EU and 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-B / # 04* / EJ to EJ <u>Mutual recognition of medical devices product licenses</u>

Introduce a mutual recognition of medical device product licenses between the EU and Japan. PMDA and MHLW should introduce a 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 will be solved quickly. Level difference between NBs should also be considered. It *should be recognized that the regulatory approval scheme of class II medical devices in Japan is far from that in the EU, i.e. no need to be reviewed by NBs for Conformite Europeenne (CE) marking of class II medical device in the EU but reviewed by NBs in Japan.*

<Yearly Status Report>

No progress / no dialogue has been seen, however, some improvements through the implementation of the new pharmaceutical and medical device law, which makes Japan accept the audit report ISO13485 issued by the countries.

Improvements are required to accept ISO14155 for clinical trials. Based on the new pharmaceutical and medical device law, some of Class II and Class III products will move to "ninsyo" application. As a result, no progress on "mutual recognition" discussions, but improvement on the speed of approvals for medical devices.

<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 time frame and with one process.
As mentioned before, it could be possible to start with lower risk, class II 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, a mutual recognition should be easy to implement.

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

Introduce a mutual recognition of clinical trial results for medical device development.
Foreign clinical trial data have been accepted as a part of application dossier when: (1) standards for conducting medical device clinical trials are set by the regulations of the country or region where the trial was performed, (2) the standards are equivalent or surpass the Japanese medical device GCP, and (3) 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 use of foreign clinical trial data for application of the 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. In this regard, the ordinance was released in December 2012 by MHLW and some improvements has been seen but in our opinion further improvements are required in the actual operation to accelerate mutual recognition of clinical trial results for medical devices. 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, Japanese government should prepare a clear definition of accepting / preparing clinical trial reports.

<Yearly Status Report>

Some progress has been seen but more progress is required as described above.

<Background>

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 time frame and through one process, ensuring high level of quality while reducing the burden on manufacturers.

Plant Protection & Biotechnology

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

Shorten review times for new applications / registrations.

<Yearly Status Report>

Some progress has been seen for this recommendation.

<Background>

Research and development of innovative and beneficial Plant Protection & Biotechnology products require high input costs. Therefore, timely access to the markets is crucial for R&D-intensive companies in order to successfully market their products and recover their initial R&D investments, which then again are used to finance further innovations.

Establishment and maintenance of science-based, predictable and timely regulatory systems free from undue political influence and the appropriate protection of proprietary data are therefore key requirements for sustainable and innovative research.

Due to the introduction of new risk assessments on humans and environment, which are necessary to secure safety and should be well-harmonized with other countries, the required investment and time for preparation of dossiers on new products are increasing. It is crucial for R&D-intensive companies to secure the time-to-market in a reasonable timeline in order to continue with innovations. Though the ministries might be working for improvement of their resources as shown in the recent change of the guideline for import tolerance application, the process in the risk assessment might be further improvable to shorten overall time for review, like a parallel review in toxicology and residue chemistry, which are currently sequentially conducted. Increase of resources both in administrative and technical reviewer areas are also crucial in order to achieve a shortening of the review time under growing requirements on safety.

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

The governments and the private sector should speed up research in Plant Protection & Biotechnology and inform consumers regularly and accurately about the state of play on GMOs, based on sound scientific knowledge. To that effect 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>

A stable supply of food is an urgent requirement. While world population keeps growing, the limits of enhancing conventional culture on existing farmlands are being reached. GMOs offer the hope of breaking these limits, but remaining doubts about their safety hamper the development of their utilisation. Considering this situation, it is an urgent matter to speed up research on GMOs and inform consumers regularly and accurately about the state of play of that research.

Animal Health

WP-B / # 08* / EJ to EJ Mutual recognition of GMP and marketing authorization for animal health products

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.

<Background>

Any 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-B / # 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 process not to interfere 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". And several member states are introducing HTA evaluation in their reimbursement systems. As such, 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 and Japan to clarify its healthcare policy and to discuss and totally improve 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-B / # 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.

<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 for 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.

Healthcare

WP-B / # 11** / 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 drug will be continued until March 2016. It is welcomed 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>

No 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 2016. 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 developments of many unapproved / off-label use drugs and forwarded those constructively. Furthermore, companies received additional requests on developments of another hundreds of unapproved / off label use drugs for several times.

However, in the FY2014 drug pricing system reform, Chuikyo concluded to postpone full-fledged implementation of the premium for new drug creation to FY2016 revision, even though the industry strongly requested. 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 FY2016 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. Abolishment 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>

No progress has been seen for this recommendation.

<Background>

The abolishment of the market expansion re-pricing was not accepted by Chuikyo even though industries insisted to eliminate the system. While the agenda for the 2014 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 "abolishment of market expansion re-pricing". Therefore, we urge to discuss this topic to abolish the re-pricing rule by market expansion in the next pricing system reform in 2016, which is contrary to the policy of evaluating pharmaceutical innovation.

3. Abolishment of the 14-day prescription rule

EU-Japan BRT members call on the Japanese government to revise the 14-day prescription rule for all new drugs.

<Yearly Status Report>

New recommendation

<Background>

Despite government's policies to promote new drug development, patient access to innovative drug is hindered by the 14-day prescription rule, which restricts the prescription lengths 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 the drug pricing system

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

<Yearly Status Report>

New recommendation

<Background>

The methods of HTA for drugs and medical devices have been discussed in Chuikyo. Although the Japanese government intends to determine the introduction of HTA system for drugs and medical devices until the medical service fee revision in 2016, the hasty and insufficient discussions may lead to the inappropriate conclusion. For instance, some countries have caused the limited patients access to innovative new drugs.

Furthermore, HTA may hinder the companies' willingness to the 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 improvement of public health.

WP-B / # 12 / EJ to J <u>Appropriate assessment of innovative values of medical devices in prices</u>**

Promote sub-dividing of the current functional classification, enhance the premiums for C1 or C2 products (class-C products) and introduce a product-based listing system for new products in order to move towards a product-based, market-oriented reimbursement pricing system in the future.

<Yearly Status Report>

In 2014, no major progress has been seen in general and major progress was made in the revision of reimbursement. More detailed division of functions into subcategories, introduction of multiple prices for medical devices of the same category as well as the abolition of the reprising system and innovation in home healthcare medical devices should be assessed appropriately.

<Background>

Different from pharmaceutical brand-oriented pricing systems, about 300,000 medical devices are classified into about 800 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 old and new products, having various realized prices, have the same reimbursement price within one functional class, which means that the price drop of old products influences the reimbursement price of new ones on the revision of the reimbursement price. This is the reason why the introduction of a product-based reimbursement pricing system is desired. In Japan's 2014 price revisions, the government's efforts to progress forward the assessment of innovative values can be seen, such as making exception of functional class rule for the excellent and innovative class-C products to keep the independent functional class within the twice price revisions. On the other hand, they strengthened the influence of foreign reference pricing. We hope the Japanese government will make further efforts to promote medical device development.

Plant Protection & Biotechnology

WP-B / # 13* / EJ to J Support research in crop breeding

Support research in crop breeding.

<Yearly Status Report>

No progress has been seen for this recommendation.

<Background>

Overall, in Japan the cooperation between governmental institutes and MNC is limited. Applied science is widely done for instance by the Plant Protection Stations (PPS) in all prefectures, however, this is not basic research. Also agricultural universities in Japan do some research on an independent basis. In the past, MAFF has spent around 400 million yen for residue trials on substances used for rice to confirm the level of the residue in rice for feed and the transfer into livestock (cow and chicken) but the ownership is with the government or some independent institutes. The project is motivated by the policy to increase food sufficiency rate. The current target of the government is a vitalization of the agriculture in general. To achieve this, a more offensive action in regard to new technologies (like application technology) is necessary.

In the future, MAFF should spend more money on basic research / fundamental technologies in order to facilitate research activities in general. In biotechnology, considerable money is spent on plant molecular biological research but the budget is recently decreasing and no genetically modified (GM) products are developed in Japan. It should be taken into consideration to develop GM rice in order to increase yield and decrease production costs. In the past, the rice genome project was supported by the government but the project has been finalized, a smaller post genome project is still running. The outcome of the project is only contribution to develop a marker assisting the breeding of rice. From such research where a considerable amount of Japanese tax payers' money is invested, yielding practical applications is desirable through co-operations among governmental institutes, universities, Japanese domestic companies and MNC. Recently, MAFF and governmental institutes are developing new breeding technologies in order to improve crop cultivars.

Recommendations from European industry

Animal Health

WP-B / # 14* / E to EJ Responsible use of antibiotics in animal health

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

<Yearly Status Report>

Progress has been seen in that the product list for 2nd line treatment has been updated on the web site of NVAL/MAFF.

<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 (FQs) 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-B / # 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 of 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>

Significant progress was made by MAFF, FSC and MHLW in shortening the withdrawal period for inactivated oil-adjuvant vaccines based on FSC's scientific assessment of dietary health impact.

<Background>

Restrictions on withdrawal period for innovative oil-adjuvant vaccines are especially stringent in Japan. Implementing scientific health risk assessment

approach in establishing the withdrawal period and increased collaboration of different ministries involved in food safety would certainly improve access of animals and animal owners to innovative animal health products which are readily available in Europe. While such global new veterinary medicinal products go already 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 aspect 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-B / # 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>

In 2014, it has been recognized that MAFF is trying to shorten the review timeline among three ministries, but it seems that MAFF is struggling to negotiate with the other two ministries. It would be appreciated if this recommendation could accelerate MAFF's initiative to deal with MHLW and FSC on this matter. It was confirmed that MAFF established the guideline to develop veterinary GMO products or products containing GMOs, however it is not clear how this guideline would affect a shortening of the review timeline.

<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-B / # 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 noticed to medical gas suppliers to obey voluntary standard by the industry. This standard is almost compatible to GMP standard. PMDA / MHLW will reinforce the GMP for medicinal gases through the PIC/S, Japan officially joined in July 2014.

<Background>

Medicinal gases are drugs or medicinal devices and have to be compliant with governmental regulations. Main regulations are national Pharmacopeia, GMP (Good Manufacturing Practices), and GDP (Good Delivery Practice). Annex 6 describes GMP and GDP for medical gases: production and distribution. The currently loose interpretation of GMP in Japan along with relatively low standards of Japanese Pharmacopeia is of lower standards as 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-B / # 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 available to patients earlier in Japan. MAFF, MHLW and FSC should start harmonized ways to shorten review times.

<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 for delay of the start for patients' enrolment in Japan.

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

For imported vaccines, national tests in both Japan and manufacturing sites have been conducted (for more than 20 years in some cases). 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 done 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.