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
(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
CAS	Chemical Abstracts Service
CE	Conformité Européene
CEFP	Council on Economic and Fiscal Policy
CHUIKYO	Central Social Insurance Medical Council
ECPA	European Crop Protection Association
EFPIA	European Federation of Pharmaceutical Industries and Associations
EPA	Economic Partnership Agreement
ESA	European Seed Association
EU	European Union
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
LLPs	Long-listed products
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
PMP	Price Maintenance Premium
PPS	Plant Protection Station
QALY	Quality-adjusted life years
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

Introduction

Japan and the EU face many similar challenges, such as aging populations, shifting demands for products and services, and rising costs in many aspects of the welfare system. Life sciences and biotechnologies offer the possibility of technologies that will help address these challenges.

Working Party 2 focuses on the following sectors:

- Healthcare (pharmaceuticals, medical devices etc.)
- Life Science & Industrial Chemicals
- Plant Protection & Biotechnology
- Animal Health

The 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. The focus is on measures that will enhance efficient healthcare practices, food technology and supply, and biotechnology.

The conclusion of the Economic Partnership Agreement in 2017 was a major achievement for both sides, and will bring mutual economic benefit. But under the headline and in-principle agreements there is much work to be done to deliver the specific improvements needed to bring our economies closer together. If the signing of the EPA marks the end of the current phase of deregulation and harmonization, then we will have wasted an opportunity to maximize the benefits for our industries and our citizens.

These once a year meetings are useful, but their value is limited without active follow-up between them. Our Working Party would like to see the creation of working-level government teams, on both the EU and Japan sides, to proactively monitor and drive progress throughout the year. Membership of the teams could perhaps be based on the EPA teams. And these teams should be tasked with developing and delivering on a plan and timelines.

Too many of the recommendations in this report have seen too little progress for too long. Instead of an ending, the EPA should be seen as a beginning. It should be a launch pad: a chance to renew our commitment to removing barriers to business; a chance to find new energy for strengthening our economic relationship; a chance to find new energy for strengthening our economic relationship; a chance to deliver on the recommendations in this report. Let us take those chances.

An asterisk (*) identifies “priority” recommendations.

Recommendations from both European and Japanese industries

HEALTHCARE

WP-2 / # 01* / EJ to EJ

Progress on mutual recognition for Pharmaceuticals GMP should be further extended

Despite the achievement of the Economic Partnership Agreement (EPA), there remain two concerns about the Mutual Recognition Agreement (MRA) on Good Manufacturing Practice (GMP) between the EU and Japan:

(i) Products derived from human cells, including blood products and several vaccines, are not covered by the MRA.

(ii) In the details of the MRA, there are still some grey areas where it is not clear which products are covered and which are not.

It is recommended here that the scope of the MRA be expanded to include products derived from human cells, and that government and industry work together to provide greater clarity on exactly which products are covered by the agreement.

<Recent Progress>

Major progress: the previous recommendation from the pharmaceutical industry was that the MRA on GMP between the EU and Japan should be expanded to include various pharmaceutical dosage forms such as ointments, injectables, sterile forms and APIs, as well as biological products, in order to avoid redundant inspections and testing. With the finalization of the text of the Economic Partnership Agreement between the EU and Japan on 8 December, 2017, much of this was achieved. Overall, the industry welcomes the finalization of the EPA and the expansion of the scope of the MRA on GMP. However, there remain the two concerns, listed above, and in addition the proper implementation of the agreement will be needed to make sure that industry and patients can fully benefit from the negotiated outcomes.

<Background>

In 2002, the EU and Japan introduced the MRA on the GMP of medical products, but it covered only the then 15 EU countries and its subjects were only non-sterile oral tablets and capsules. In April 2016, the MRA was expanded to cover all the now 28 EU countries, and expansion of subjects to other formulations of medical products was discussed as part of the EPA agenda.

In March 2017, the EU and the US announced that they had agreed on an MRA for GMP, and this came into effect on 1 November. Oral tablets, capsules, ointments, injectables, API, and biological products are included in this agreement. Human vaccines and plasma derived products are not immediately included within the operational scope of the agreement, but their inclusion will be considered by no later than 15 July 2022.

WP-2 / # 02 / EJ to EJ
Mutual recognition should be improved for Medical Devices

(i) Mutual recognition of quality management audit results for Medical Devices should be established between EU and Japan

The EU and Japanese governments should establish a mutual recognition scheme for Quality Management System (QMS) audit results. Japan is a member of the Medical Device Single Audit Program Pilot (MDSAP), through which it shares QMS audit results with the United States, Canada, Australia and Brazil. There should be either: (i) a similar regulatory harmonisation approach between the EU and Japan; or (ii) the EU should also become a member of MDSAP, in order to avoid occasional QMS disputes with the Japanese authorities when the ISO13485 evaluation report from the EU is poor or insufficient. If the EU were to join MDSAP, the below-listed issues would be addressed.

Although the ISO13485 audit report is now accepted in Japan for the QMS process as a result of the 2014 J-PMD Act, and the inspection burden has decreased somewhat as a result, the QMS inspection process is still complicated and burdensome.

- For example, there is still a requirement for the Japanese original document. Submission-related formats and standards need to be harmonized.
- In addition, there remains a requirement for a post-approval QMS inspection application to be submitted to PMDA for each product (or product family) every five years after approval, yet the approval dates vary by product and renewal management is cumbersome with potential risk of an oversight. Post-approval QMS inspection date should coincide with the renewal of marketing authorization so as to simplify and assure proper renewal operation.

The EU industry side requests a complete harmonization by eliminating Japan's deviations on top of ISO13485. As a next step, mutual recognition of Medical Devices 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 industry side would also like to suggest the necessity of disseminating official information on QMS ministerial ordinances in English, for the purpose of MDSAP rationalization of investigation pursuant to Chapter 3, Production and Marketing.

<Recent Progress>
No further progress since Japan introduced the J-PMD Act in November 2014, and joined the Medical Device Single Audit Program Pilot (MDSAP) in 2015.

<Background>
In June 2015, the Japanese government announced it would officially join MDSAP, an international cooperation programme for quality assurance of medical devices by the United States, Canada, Australia and Brazil as members. 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, but under MDSAP a single QMS audit result is valid among all

member countries: this reduces the burden 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.

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.

(ii) There should be mutual recognition of Medical Devices product licenses

Mutual recognition of Medical Devices product licenses between the EU and Japan should be introduced. Regulations of low risk class II devices are similar in the EU and Japan, and therefore mutual recognition of this category of products is possible. PMDA and MHLW should introduce mutual recognition, taking into account the difference of classification of medical devices between Japan and the EU. By harmonizing QMS and classification it should be possible to introduce new products within the same time frame and in one process.

The EU should better communicate with the Japanese government about the new Medical Device Regulation (MDR) implementation. The EU will pursue MDR, but not enough information is being communicated to the Japanese side.

<Recent Progress>
The PMDA's overall performance has been improved to shorten approval times for medical devices, but further improvement is possible. To date, in terms of mutual recognition for product licences no progress has been seen. However, the PMDA's five-year Examination Acceleration Cooperation Plan is expected to be completed in 2018, after which there should be a system and procedures where industry is able to continuously monitor the certification performance so that any improvement necessary can be easily addressed without delay.

<Background>
The evaluation schemes between the Medical Devices Directive of the EU and J-PMD Act are quite similar:
- 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.

(iii) There should be mutual recognition of clinical trial results for Medical Devices

Mutual recognition of clinical trial results for the development of new Medical Devices should be accelerated. This would support the availability of new products to patients in Japan and the EU within the same timeframe and through one process; it would shorten the "device lag", ensure a high level of quality, and reduce the burden on manufacturers.

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 already mutually recognized between the EU and Japan. EU-Japan BRT members request that both the EU and Japan accelerate mutual recognition of clinical trial results in actual operation, where the conformity is currently insufficient due to the exiting strict conditions applied when accepting clinical evaluation reports from outside of Japan.

More specifically, 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 ISO14155 should be easily accepted and if not accepted, a valid explanation with a scientific background is a must. In addition, the Japanese government should prepare a clear definition for accepting and preparing clinical trial reports.

Furthermore, 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. Early disclosure of clinical trial-related guidance would promote the entry of overseas companies to the Japanese market. Regarding the guidance for the preparation of the Clinical Evaluation Report, we request the Japanese Government to issue the guidance as early as possible.

It is expected that the Japanese Government will develop guidelines for effective utilization of clinical evaluation reports soon. The EU industry side requests that the Japanese government respond with specific timelines for this action as this has been a previously listed request with no practical progress.

<Recent Progress>
While the EU moved from MDD (Medical Device Directive) to MDR (Medical Device Regulation) in 2017, it is premature to judge whether this will lead to an equivalent level of clinical evidence as seen in the US FDA, and may therefore accelerate the mutual recognition of clinical trials with Japan. It is key is to closely monitor how this progresses under the MDR environment.

In June 2016, the EU published the fourth revision of guidance "Clinical evaluation: A Guide for Manufacturers and Notified Bodies under Directives 93/42/EEC and 90/385/EEC (MEDDEV 2.7/1 revision 4)". The guidance focused much more on the applicability of the clinical data rather than its origin. In general, foreign clinical data is accepted in the EU for conformity assessment by Notified Bodies if certain criteria are met, such as e.g. an analysis whether data generated outside the EU is transferable to the EU population.

<Background>
Differences in the definition of GCP between Japan and the EU currently prevent the general use of non-Japanese clinical trial results in the application for new medical devices in Japan. However, foreign clinical trial data has been accepted in Japan 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 standards or considered to have

an equivalent level of quality. Even in these cases, additional data has sometimes been required with unclear reasons.

More positively, the Japanese government encourages active use of the advance consultation service provided by the Pharmaceuticals and Medical Devices Agency (PMDA) on individual medical device applications, to address the use of foreign clinical trial data for the application of a device. A similar situation exists in Europe, where there is no general ability to use Japanese clinical data but some cases where clinical trial results acquired in Japan have been applied to the new medical device applications in the EU.

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.

PLANT PROTECTION & BIOTECHNOLOGY

WP-2 / # 03 / EJ to EJ
Legal clarity for and appropriate regulation of Plant Protection innovation, including GM and gene-edited plants.

The EU and Japan governments should regulate agricultural technologies – including crop protection, GM and gene-edited crops – in a science-based and proportionate manner. They should work with industry and other stakeholders to increase trust in the regulatory science and societal acceptance. Specifically:

- Both the EU and Japan should advance and adhere to global harmonization on GMO risk assessments, and support the Global Low Level Presence Initiative.
- Both the EU and Japan should provide legal clarity on the status of techniques such as genome editing – which are relevant not only for plant breeding – and preferably in a harmonized manner.

We call for inclusive, fact-based platforms for dialogue, information sharing and trust-building in both geographies, aiming at a risk-proportionate, predictable, science-based and non-discriminatory treatment of new technologies.

<Recent Progress>
No major progress has been seen for this recommendation.

<Background>
In December 2017, 17 governments including Japan (but not the EU) warned that: *“Our farmers' choice of safe tools is increasingly undermined by regulatory barriers that lack a sufficient scientific justification, and this is having substantial negative impact on the production of, and trade in, safe food and agricultural products”*.

The absence of a science-based and proportionate regulatory approach to agricultural technologies inappropriately hinders societal acceptance and facilitates misinformation. Examples of resulting problems:

(i) EU Member States and the European Parliament objecting to EU authorization of GM crops for import, despite EFSA's confirmation that they are as safe as conventional crops;
(ii) EU legislation imposing 90-day rodent studies on all applications for GM import, despite the scientific consensus (upheld by EFSA and major recent Commission-funded research projects) that these are scientifically unjustified.
(iii) In the EU, the risk assessment for a GM import authorization now takes five years and more in most cases. This is ten times as long as foreseen. According to EU law EFSA is obliged to "endeavour to respect a time limit of six months".

ANIMAL HEALTH

WP-2 / # 04* / EJ to EJ
There should be mutual recognition of GMP for Animal Health products

The EU-Japan Economic Partnership Agreement should aim for mutual recognition of European and Japanese marketing authorizations for veterinary products, starting with mutual recognition of GMP certification of veterinary medicines where the GMP requirements are similar or equivalent. Mutual recognition of GMP certification for veterinary products between the EU and Japan is important to achieve faster delivery of new useful products. MAFF and the European agency should accept the GMP certification of the other party where the GMP requirements are similar or equivalent. In future, both governments should consider mutual recognition of the EU and Japanese market authorization.

<Recent Progress>
The in-principle agreement to consider inclusions of veterinary products in the GMP MRA is welcome, but a decision to include still needs to be made and implemented.

<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 MRA on GMP for Pharmaceuticals between the EU and the US became effective on 1 November 2017. Veterinary products are not immediately included in the operational scope of the agreement, but they will be considered for inclusion by no later than 15 July 2019.

HEALTHCARE

WP-2 / # 05 / EJ to E
The UK's withdrawal from the EU should create the minimum of disruption to patients and to the pharmaceutical and cosmetic industries

With regard to Brexit, the priority of the pharmaceutical and cosmetic industries is on minimizing disruption to patients and industry. There is a particular need for

harmonization and continuity around the single regulatory system, in order to maintain a stable EU Regulatory System and smooth functioning of the European Medicines Agency for pharmaceuticals. Similarly, there should be a single regulatory regime for cosmetics with a single evaluation of the safety of cosmetic ingredients used in products in the EU and the UK. More specifically, the recommendations are:

- Regulation: Securing ongoing alignment, cooperation and mutual recognition between the UK and the EU regarding the authorization, testing and surveillance of medicines and cosmetics should be a priority outcome of the negotiations. There should be alignment on the safety evaluation of ingredients used in cosmetics and pharmaceutical products. Any differences could undermine the credibility of the EU and UK agencies.
- People: Providing certainty for EU and UK citizens working in the pharmaceutical and cosmetic industries. Agree a straightforward immigration system that allows companies to employ the best talent from around the world, and that facilitates skilled UK and EU nationals working across Europe.
- Research: Scientific research collaboration between the UK and EU should be maintained after the UK leaves the EU. UK/EU scientific collaboration strengthens the EU's global position in life sciences, attracting global life science investment to the EU.
- Intellectual Property: Equivalent standards of IP should continue to apply in the UK after Brexit and the existing level of strong IP incentives across the EU should be maintained.
- Trade and Supply: Medicines and cosmetics used by patients across Europe have integrated supply chains, which includes the UK. The UK and the EU should conclude a comprehensive agreement with a pharmaceuticals/cosmetics protocol that ensures full alignment between EU and UK legislation. Any such agreement needs to avoid causing any disruption to existing quality control arrangements and must not disrupt the supply of medicines to patients in Europe or the UK.

<Recent Progress>
Negotiations between the EU and the UK are ongoing.

<Background>
In June 2016, the citizens of the United Kingdom voted in a referendum to leave the European Union. The UK will officially leave the European Union on 29 March 2019, although a transitional deal until the end of 2020 is probable and may mean that little changes until after that date.

PLANT PROTECTION & BIOTECHNOLOGY

WP-2 / # 06 / EJ to E
Regulations governing import Maximum Residue Limits (MRLs) into the EU should be clarified so as to allow free trade of food commodities

There is potential contradiction between REGULATION (EC) NO 396/2005, which governs import MRLs, and REGULATION (EC) NO 1107/2009, which governs market authorization of plant protection products in Europe. BRT members are concerned that the latter regulation is influencing import MRLs, as it introduced hazard cut-off criteria which can eliminate substances from the market. There may be cases where an import MRL regulated under REGULATION (EC) NO 396/2005, is beyond the cut-off level

established under REGULATION (EC) NO 1107/2009, and substances which have been assessed as safe under the first regulation might be banned by the second. The regulations should be clarified, based on sound science, so as to facilitate free trade.

<Recent Progress>
In September 2017, 17 countries signed a joint statement on pesticide MRLs at the 11th World Trade Organization (WTO) Ministerial Conference in Buenos Aires, Argentina. The joint statement reinforced the importance of science-based standards under the WTO Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement), and recognized the increase of MRL-related issues faced by farmers around the world. Members reiterated their support of the following:

- *Increasing the capacity and efficiency of Codex in setting international standards on pesticide MRLs*
- *Achieving greater harmonization across national and regional MRLs*
- *Enabling greater access to alternative pesticides and pesticides for minor-use crops*

The EU has invited its trading partners to help evaluate EU pesticide legislation. In November 2017, the European Union notified the WTO of an invitation to all WTO members to contribute to an evidence-based evaluation of Regulation (EC) No 1107/2009 and Regulation (EC) No 396/2005. This online survey was open until 31 December 2017, and the report is expected to be completed in early 2019. Japan's Ministry of Agriculture, Forestry and Fisheries (MAFF) participated in the survey.

<Background>
In the absence of necessary import MRLs, food commodities containing the residue of the active substance are prohibited for importation even though the said substance is approved in the exporting country and the residue does not cause any harmful effect on human health. Excessive protection measures for food safety should be avoided in order to facilitate international trade. 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.

HEALTHCARE

WP-2 / # 07* / EJ to J
Reform of the pharmaceutical pricing system should provide a stable, predictable environment that rewards innovation

The EU-Japan BRT members call for a fresh review of the new system to find ways to strengthen the reward for innovation, maintaining an incentive for companies to develop new drugs and bring them rapidly to Japan and thereby giving Japanese patients early access to the latest treatments. The changes announced in December 2017, to be introduced in April 2018, will significantly reduce the support for innovation and risk the reopening of the "drug lag". Patients in Japan will be negatively impacted if that happens. Specifically, we propose that the Price Maintenance Premium (PMP) system should be expanded to cover all innovative products, including incremental innovations, during their patent exclusive period, and implemented at the next drug pricing system reform in April 2020. Under the new system introduced in April 2018,

application of the PMP is largely dependent on the timing of launch, how the drug was evaluated in the initial pricing, and the past record of company performance: but in many cases these are poor ways to assess the degree of innovation of the product. The proposal to expand the PMP is perfectly consistent with overall budget management if savings are made elsewhere in the drug budget and the non-drug healthcare budget.

It should be noted that a "drug lag" may not be immediately observed, as pharmaceutical companies have already increased their investment in drug development in Japan in recent years and such investments have long lead times. The reopening of the "drug lag" may take several years before it becomes visible. Therefore the EU-Japan BRT members call on the Japanese authorities to understand this situation and to avoid further pricing system reform until the full impact of the 2018 changes can be seen.

<Recent Progress>
The changes announced in 2017 and implemented on 1 April 2018 will have a significant negative impact on the industry and on Japanese patients' access to the latest innovative drugs.

<Background>
The Chuikyo discussed "fundamental" drug pricing system reform over 2017, with the revised system to be implemented from April 2018. The reform announced in December 2017 greatly disappointed the pharmaceutical industry and brings into question Japan's support for innovative medicines. The EU-Japan BRT members had strongly called for the review to lead to a system which appropriately evaluates and rewards innovation, maintaining an incentive for companies to develop new drugs and bring them rapidly to Japan and thereby giving Japanese patients early access to the latest treatments.

The main area of disappointment has been in changes to the Price Maintenance Premium (PMP), where the criteria for qualification have been significantly narrowed. In addition, an index has been created to rank companies based on their contribution to new drug development, a limited and inexact measure of a company's commitment to bringing innovation to Japan. Companies in the top category will get 100% of the value of the PMP for their products, but those in the next category only 90% and those in the third category only 80%. The proportion of companies able to qualify for the top category will be "25% but not exceeding 30%, even if there are many companies with the same score".

Other changes include:
- Comparator pricing method I (CMI): comparison will be made to the full price, not the "price minus PMP portion". CMII products will be compared with "Price minus PMP portion". This will be reviewed again for the 2020 reform.
- New indications: quarterly reviews for any products with annual sales greater than Y35bn (=266m euros).
- Annual repricing for products discounting beyond a certain rate (or certain value threshold – it is still not clear), but the decision on the criteria for product selection has been postponed.

- Foreign Price Adjustment: the US price will still be referenced if there are ASP/NDAC prices available.
- Long Listed Products (LLPs): more rapid price reductions.
- Cost Effectiveness Analysis (CEA)/Health Technology Assessment (HTA): price adjustments on the premium part of the drug price will be made in April 2018 based on the trial CEA analysis results.

The fundamental drug pricing system reform will make savings from both innovative and off-patent drugs. Unless innovation is properly evaluated, it will become very hard for the industry to continuously create new drugs to fulfil unmet medical needs. This will not be beneficial for patients or for society.

WP-2 / # 08 / EJ to J
<u>The 14-day prescription rule for Pharmaceuticals should be abolished</u>

Japan should abolish the 14-day prescription rule, which has been superseded by more recent and more robust safety measures. Should this not be possible, as a minimum the prescription limitation should be extended to 30 days and the period shortened to 6 months, instead of the current 12 months.

<Recent Progress>
No major progress has been seen for this recommendation.

<Background>
In 2015, the government's own Regulatory Reform Council recommended abolition of this rule. However, in July 2016 the Chuikyo decided that the rule was necessary, and the government subsequently announced rejection of this recommendation. In April 2017, the Regulatory Reform Council requested again the discussion of this issue at Chuikyo. However, in December 2017, Chuikyo concluded without any discussion that the current rule should be maintained.

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. In practice this 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, and hence the 14-day rule is no longer necessary. The latest decision by the Chuikyo to maintain the status quo, without proper discussion, was highly regrettable - BRT members continue to recommend abolition of this rule in order to provide better patient access to innovative new drugs.

WP-2 / # 09 / EJ to J
Japan should improve its environment for innovative Medical Devices

(i) Japan should further sub-divide the current functional classification for Medical Devices

Japan should further sub-divide the current functional classifications in order to improve the reward for innovation. Currently, the various products within a functional class, which may have varying market prices, all have the same reimbursement price. This results in price reductions for old products influencing the reimbursement price of new products. In order to appropriately reward innovation in Medical Devices, the reimbursement price of new products should be set separately from the price of old products.

The reimbursement pricing system should be revised so that it is closer to a product-oriented system. When moving closer towards a more product-oriented reimbursement system, it is sensible to allow a certain period of time prior to conclusive assessment, as the effectiveness of new products often takes time to become apparent, and for safety and efficacy to be adequately assessed. The results of these assessments should also be reflected in efforts to approve the reimbursement system. Any meaningful upgrade or improvement of a product should be properly evaluated and classified based on a clear definition, if not categorized under a new functional classification. The same should also apply to next generation products with the same functionality.

<Recent Progress>
Minor progress. At the revision of medical service fees in 2016, the functional classifications were reviewed and 852 classes were set, up from 844 classes, or less than a 0.1% increase. The exceptional rule of the functional classification remains.

<Background>
Different from pharmaceutical pricing systems, about 280,000 Medical Devices are classified into about 900 functional classes in Japan, and one reimbursement price is then set for one functional class, based on structure, intended use, effectiveness etc.

(ii) Japan should abolish the foreign price reference system for Medical Devices

The foreign price reference system for Medical Devices in Japan should be abolished because: (i) the average price in Japan is already only 80 per cent of foreign prices, according to MHLW documents; and (ii) the upper limit of the price variance between foreign countries and Japan no longer makes sense in reality. The Japanese government makes frequent modifications to the foreign price adjustment system, so it should be possible to implement the recommendation stated above quickly.

<Recent Progress>
No major progress has been seen. 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 highly decentralized in Japan.

WP-2 / # 10* / EJ to J
Health Technology Assessment (HTA) should be introduced with caution so that it does not become a barrier to patient access

(i) As the Japanese drug pricing system already incorporates the concept of HTA, Cost Effectiveness Analysis (CEA) HTA for Pharmaceuticals should be introduced cautiously and only after thorough evaluation of its necessity.

- If CEA/HTA is to be introduced in Japan, it should be positioned as being supplemental, based on the current drug pricing system.
- Assessment should not be based on a single measure such as the Incremental Cost Effectiveness Ratio (ICER), since this does not reflect the full value of a medicine and is highly dependent on the assumptions made. Ethical and societal considerations should have more weight in final results.
- All stakeholders, including experts from industry, should fully participate in the discussion of CEA to ensure that the experiences and failures of other countries are duly evaluated before introduction.

<Recent Progress>
Some grounds for concern. The results of the trial introduction of HTA as applied in April 2018 suggest it is just another cost-containment tool. The shape of the permanent system remains unclear.

<Background>
Seven pharmaceutical products underwent trial assessment for cost effectiveness from 2016, and were repriced based on this assessment in April 2018. Originally, the trial introduction should have ended and full implementation to start from April 2018. However, there were many troubles in the process and it was decided to continue the trial introduction and postpone full implementation to the end of FY 2018.

The need for caution in the introduction of any HTA system is because:
- In Japan, the NHI drug pricing system already includes the concept of HTA. Additional clinical benefits of new medicines are evaluated from multiple angles such as efficacy and safety. If the benefits are recognized, they are rewarded with price premiums.
- None of countries that have introduced Cost Effectiveness Assessment HTA has such detailed drug pricing rules as Japan's. Those other countries use the result of Cost Effectiveness Assessment to judge the appropriateness of prices requested by pharmaceutical companies. In Japan this is unnecessary as the price

is not simply requested by the company but is calculated using the government's mechanism.
- Total drug expenditure in Japan is already sufficiently well-controlled by the current pricing system.

(ii) HTA for Medical Devices should be introduced with caution

Japan should be cautious in the introduction of HTA (health technology assessment) systems for Medical Devices, taking into account the following factors:
- QALY, a sort of HTA evaluation index for pharmaceutical products, cannot be applied for evaluation of medical devices
- users' skills and techniques of each medical device can affect the evaluation
- medical devices have a shorter improvement cycle than pharmaceuticals

It is important that HTA systems do not hinder the creation of innovative products, delay the listing for medical insurance reimbursement, or impose an excessive burden on the industry (e.g. development of databases or human resources). Such outcomes would delay patient access to cutting-edge medical technologies. To avoid this, there should be a clear distinction and balance between "assessment" and "appraisal". There should be no inappropriate use of the ICER measure, with pre-determined thresholds and pricing controls.

<Recent Progress>
Five medical device products have been under trial assessment of cost effectiveness since 2016. Detail method of application of the results is under discussion at Chuikyo.

<Background>
In April 2016, the Japanese government launched a trial HTA system that included assessment of some Medical Devices.

PLANT PROTECTION & BIOTECHNOLOGY

WP-2 / # 11* / EJ to J
Review times for Plant Protection & Biotechnology products should be shortened

The introduction of parallel review by MAFF (Ministry of Agriculture, Forestry and Fisheries) and the FSC (Food Safety Commission) in 2016 offers the potential for a major improvement in the time taken to review and approve new products. The priority is now to assess if the new process is working as intended in practice.

There may be other possible ways to shorten review times:
- 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 on the Japanese authorities.

<Recent Progress>
There was major progress in 2016, with the introduction of parallel review by MAFF and the other authorities responsible for risk assessment (MHLW, the FSC and the

Ministry of the Environment). This has the potential to reduce the registration process by 150 days, but it will take time to see if the expected improvement is realized.

<Background>

Delivering novel and safe Plant Protection products and seeds is very important if the needs of the growing world population for high quality foods and feeds are to be met. While R&D-intensive companies are continuously and heavily investing in new 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.

If it works as planned, the new approval system should bring Japan much closer to international best practice, with an expected average approval time of 21 to 27 months (versus 27 to 36 months before the 2016 change). However, in the US and Korea the time taken for review is 18 to 24 months, so it may be possible to make further progress.

Recommendations from European industry

HEALTHCARE

WP-2 / # 12 / E to J
Requirements for Japanese versions of the clinical trial protocol and investigators brochure should be relaxed

In Japan, the clinical trial protocol and investigator's brochure is required in Japanese, and translation from English is therefore required for clinical trial notification in Japan. This raises the cost and delays the timelines for clinical trials in Japan.

The acceptance of English-only materials for global clinical trials performed in Japan would require 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 earlier to patients in Japan.

<Recent Progress>
In January 2018, both EFPIA and PhRMA submitted documents to the Cabinet Office's Regulatory Reform Promotion Council, requesting the acceptance of English language documents for certain Post Marketing Surveillance (PMS) activities (e.g. database) and clinical trial reports. Discussions between the two associations and the government are ongoing about the acceptance of English documents.

<Background>
The requirement for translation from the original English version for clinical trial notification of global trials in Japan is considered to be a cause of delay to the start of patients' enrolment in Japan.

LIFE SCIENCE & INDUSTRIAL CHEMICALS

WP-2 / # 13 / E to J
English translations for issued regulations

METI (Ministry of Economy, Trade and Industry) & MHLW (Ministry of Health, Labour and Welfare) should provide English translations for issued regulations.

<Recent Progress>
No major progress has been seen for this recommendation.

<Background>
Currently, METI and MHLW provide English translations of issued regulations only in limited cases. This holds true for new laws, enforcement ordinances, enforcement regulations, official notices, guidelines and similar communication published by the ministries. Consequently, to ensure regulatory compliance, companies with activities outside Japan need to translate by themselves such regulations to be able to align internally with non-Japanese-speaking stakeholders. This results not only in additional

efforts in each company, but also creates a risk of differing interpretations by each company based on their own translations.

In other Asian countries, such as Korea, regulating authorities provide English translations at the same time as, or shortly after, announcements in the local language. Japan should adopt a similar approach, thereby ensuring consistent compliance with regulations and enhancing Japan's presence in the global marketplace.

WP-2 / # 14 / E to J
Provide a reference to CAS numbers in regulations for Chemical substances

METI and MHLW regulations should refer to Chemical Abstracts Service (CAS) numbers in addition to chemical compound names.

<Recent Progress>
No major progress has been seen for this recommendation..

<Background>
CAS provides a unique identifier for chemical substances and is nowadays used by most companies in their internal processes to ensure regulatory compliance. However, the regulations in Japan currently only list the names of concerned chemical substances without indicating respective CAS numbers. These include the Poisonous and Deleterious Substance Control Law (PDSCL), the Industrial Safety and Health Law (ISHL) and the Pollutant Release and Transfer Register (PRTR).

As a result, in order to assess the relevance of any new regulation, each company needs to individually map CAS numbers to the chemicals listed in published regulations. This results not only in additional efforts by each company, but also induces risk of differing interpretations by each company and consequently varying degrees of regulatory compliance.

It has become standard for authorities in the EU and US to indicate CAS numbers in issued regulations. Also in other Asian countries, such as Korea, China and Taiwan, regulating authorities already reference CAS numbers in their announcements. Japan should adopt the global practice of indicating CAS numbers in issued regulations to ensure swift and accurate internal alignment of concerned companies.

WP-2 / # 15 / E to J
Align naming requirements for product labels of chemicals with the names used in Japanese law

MHLW should revise PDSCL labelling requirements to indicate chemicals in accordance with the naming used in Japanese law.

<Recent Progress>
No major progress has been seen for this recommendation.

<Background>
Japanese law regulates chemical substances mostly by chemical group and only in exceptional cases by specific name. Regulations such as ISHL and PRTR require that labels for products containing chemical substances name these substances “as regulated by the Japanese law”. However, only the PDSCL requires that labels of products containing related chemical substances always state the specific names of the included chemical substances. From a user perspective, it is easier to work with descriptions such as “Organic Cyanide Compound” (chemical group name) than “2-Methyl-6-oxo-1,6-dihydro-3,4'-bipyridine-5-carbonitrile” (specific name of the chemical substance). Discrepancies between naming in Japanese regulations and product labelling requirements creates a risk that substances are used without a clear understanding of the regulations they relate to.

Japan should renew the PDSCL so that product labels must list contained chemicals in the naming “as regulated by the Japanese law” instead of “by specific chemical substance name”. This would allow users to quickly assess the toxicity and regulatory relevance of the materials they handle.

(Document ends)