APPENDIX 2004.3.

Pharmaceutical Administration and Regulations in Japan

http://www.jpma.or.jp/jpmalib/2003pdf/yakuji03.pdf

http://www.jpma.or.jp/12english/parj/index.html

This Appendix to Pharmaceutical Administration and Regulations and in Japan was prepared by the English RA Information Task Force of JPMA. The Task Force is solely responsible for the contents of this file.

English Regulatory Information Task Force

JAPAN PHARMACEUTICAL MANUFACTURERS ASSOCIATION (JPMA)

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Appendix 1 Revision of Pharmaceutical System

Source: Pharmaceutical Manufacturing Manager's Training Course, September 2002

General explanation

1. Revision of the Pharmaceutical Affairs Law

The following three main revisions in the pharmaceutical system were made in the amendment of the Pharmaceutical Affairs Law enacted on July 31, 2002.

(1) Augmentation of safety assurance policies in this century of biotechnology and genomics

(2) Radical revision of safety policies for medical devices

(3) Augmentation of post-marketing safety policies and revision of the approval and licensing system

Augmentation of safety assurance policies in this century of biotechnology and genomics includes the system for biological products consisting of important measures to assure safety based on a definition of biological products, classification of products based on the risk of infection and the characteristics of biological products. This system was enforced on July 30, 2002.

The draft of government ordinances on augmentation of post-marketing safety policies and revision of the approval and licensing system was opened to public comment from June 17 to August 17, 2002 and a wide range of opinions were collected.

The invitation of public comments for the revised GMP was extended to August 29. At present, the opinions are being used as a reference for a revision of the Pharmaceutical Affairs Law. The ordinance for revision will be issued this autumn and the revised Pharmaceutical Affairs Law will be enforced in 2005.

2. Establishment of the General Organization for Drugs and Medical Devices

After the bill was passed at the end of 2002, preparations have been underway to establish the General Organization for Drugs and Medical Devices on April 1, 2005.

The new organization will first initiate a new system to provide relief for health damage including infections related to biological products once new safety measures for biological products are in force.

The system will be established to coincide with the enforcement of the revised Pharmaceutical Affairs Law in 2005.

The review system is under investigation based on the following points:

(1) Unification of clinical trial consultations and reviews

(2) Assurance of better quality reviews, transparency of the review process and shortening of

the review period.

(3) Introduction of a fast-tract clinical consultation system and augmentation of the fast-tract (priority) review system.

The following points to strengthen safety measures are also under investigation.

(1) Unification of collection of adverse drug reaction (ADR) reports by the new Organization and understanding of important safety-related information by the Ministry with no leaks

(2) Qualitative improvement of surveys, analysis and evaluation of safety information

(3) Augmentation of the consultation system for companies

(4) Augmentation of the information dissemination system

The government plans to take measures to secure funds required for the augmentation and strengthening of these systems, and also plans to increase review fees and collect contributions for new safety measures.

In the future, coordination with related persons will continue and preparations are being made to establish an organization, which is highly specialized, transparent, neutral and efficient in keeping with an independent administrative corporation.

3. Quality reevaluation

Quality reevaluation for generic products was established in February 1997 to assure reliable quality including dissolution of oral solid products. Dissolution specifications of oral solid products are gradually being established and the suitability of the generic products is being confirmed. On an annual production basis, more than 95% of generic products have been designated for quality reevaluation and quality reevaluation has been competed on about 80% of the products (250 ingredients in 2,140 products as of August 2003).

The 16th edition of the Orange Book containing the results of reevaluation of each of the products for which quality reevaluation has been completed and the dissolution test specifications compiled was published.

Work on the remaining products continues and completion is expected in 2004.

4. Handling non-prescription products

Standards concerning the ingredients and quantities, dosage and administration, and indications of nonprescription drugs are designated after hearing opinions of the Council on Drugs and Food Sanitation. The approval authority for 14 therapeutic categories including cold remedies and antipyretic analgesics that can be reviewed uniformly based on these standards has been transferred to the prefectural authorities.

In addition to review of individual products based on approval precedents in cases where approval authority has not be shifted to local authorities, approvals of non-prescription drugs

containing new ingredients (direct OTC drugs) and drugs containing ingredients transferred from prescription to non-prescription drugs and not used previously in non-prescription drugs (switch OTC drugs) are decided by reviews of efficacy and safety by the Council on Drugs and Food Sanitation.

In November 2002, the Council on Reform of Non-prescription Drug Approval Reviews published its interim report. Based on this report, revisions were made to rationalize application categories and attached data. From October 1, 2003, the previous six application categories were reduced to four. The MHLW notification on confirmation of data from safety studies by the time of approval was revised on August 27, 2003.

5. International Conference on Harmonization (ICH)

Guidelines are being prepared in order to speed up approval reviews as much as possible for excellent drugs developed worldwide under an international system by the EU, Japan and the United States. As of August 2003, 54 guidelines had been published with contents approved by regulatory authorities in each region including Japan.

At the 5th ICH held in San Diego in the US in November 2000, final agreement was reached on the Common technical Document (CTD) intended to standardize the format and contents of data to be attached to approval applications, the most important topic tackled at ICH.

Expert Working Groups of the ICH Steering Committee held meetings in Tokyo in May 2001, in Brussels in February 2002, in Washington in September 2002, in Tokyo in February 2003 and in Brussels in July 2003.

New ICH topics include the electronic CTD (e-CTD), comparisons of equivalence of biotechnological products, post-marketing safety policies, clinical evaluation of QT prolongation in ECGs and drugs for gene therapy. The 6th ICH was held in Osaka in November 2003.

6. Progress of information technology (IT)

With the computerization of applications, notifications and other procedures, all administrative procedures specified by the government actually became possible via the Internet by 2003 based on the “e-Japan priority plan” (established by the High Level Information Transmission Network Society Promotion Strategy Headquarters in March 2001). The foundation for an electronic government with paperless procedures including applications and notifications was laid.

The current floppy disk (FD) application and review system for drugs is the core system for applications and notifications based on the Pharmaceutical Affairs Law. An on-line interface system for drug application and notification procedures is now under construction. This system brings together the current FD system and various systems required for electronic applications including the MHLW in-house universal processing system for applications and notifications that

receives applications by Internet. Preparations are now underway with the aim of starting operation in March 2004.

Although it will become possible to file applications and submit notifications via the Internet in 2003, future applications and notifications can still be handled by the conventional FD application system via the prefectural pharmaceutical authorities in the future.

Revisions of the pharmaceutical system

I. Government ordinances and notices based on revisions of the pharmaceutical system

Cabinet orders, ministerial ordinances and notices have to be issued without delay to assure smooth operation of the system based on the revision of the Pharmaceutical Affairs Law amended by the Law for Partial Revision of the Pharmaceutical Affairs Law and Blood Collection and Donation Services Control Law promulgated in July 2002 (Law No. 96, 2002). Part of the revised Pharmaceutical Affairs Law, including the provisions related to biological products, came into effect from July 30, 2003. The part of the Law concerning business licenses and approvals was open to pubic comment from June to August 2003 and many opinions were submitted. At present, work related to enforcement is underway.

II. Revision of other laws and ordinances related to revision of the Pharmaceutical Affairs Law

Other laws and ordinances related to revision of the Pharmaceutical Affairs Law that must be revised by July 30, 2003 or July 2005 are as follows.

- Related laws and ordinance enforced on July 30, 2003

(1) Pharmaceutical Affairs Law Enforcement Ordinance (export exemptions and exemptions for drugs granted special licenses before approval)

(2) Pharmaceutical Affairs Law Enforcement Regulations (biological products, ADR reports from medical institutions, medical institution and investigator initiated clinical trials

(3) Revision of other ministerial ordinances

a) Ordinance on standards for conduct of medical institution and investigator initiated clinical trials (partial revision of current GCP ordinance)

b) Structural and equipment regulations for pharmacies, etc. (provisions related to manufacturing plants for specified biological products)

c) Manufacturing control and quality control regulations for drugs and medical devices (GMP) (retention of manufacturing records)

(4) Newly issued and revised notices

a) System for designation of biological products and specified biological products

b) Establishment of standards for raw materials derived from living organisms (Article 42 of the Pharmaceutical Affairs Law)

c) Partial abolition of notices for designation of drugs for which records must be kept (drugs specified in Article 11-3, Paragraph 1 of the Enforcement Regulations)

d) Revision of notices designating medical devices requiring labeling of manufacturing number or manufacturing codes (addition of biological products)

(5) Others (enforcement notifications)

a) Guidelines for preparation of package inserts of biological products

b) Approval standards for biological product manufacturing managers

c) Items related to handling of other government ordinances and notices

- Related laws and ordinance to be enforced in 2005

(1) Pharmaceutical Affairs Law Enforcement Ordinance (licensing system for manufacturing businesses and manufacturing/ distribution businesses*, GMP review system, revision of the range of application of GMP, etc.)

* This refers to licenses for distribution businesses with complete outsourcing of manufacturing, which was not allowed in the past.

(2) Pharmaceutical Affairs Law Enforcement Regulations (categories of manufacturing business licenses and manufacturing plant certification, requirements for general manufacturing and distribution supervisors of medical devices, etc.)

(3) Issuing and revision of other ministerial ordinances

a) Revision of structural and equipment regulations for pharmacies, etc.

b) Establishment of safety control standards after manufacture and distribution [Good Vigilance Practice (GVP)]

c) Establishment of manufacturing and distribution quality control standards [Good Quality Practice (GQP)]

d) Establishment of post-marketing surveillance standards (GPSP) (separated from the conventional GPMSP; public comment to be invited in future)

e) Revision of manufacturing control and quality control regulations for drugs and medical devices (GMP) (abolition of GMPI and revision based on international harmonization; public comment to be invited in future)

f) Establishment of continuing training curriculum for medical device distributors, etc.

(4) Others

a) Items related to general manufacturing and distribution supervisors and manufacturing managers

b) Business status of approvals and licenses received to date and handling of products

c) Items related to application of other government ordinances, ministerial ordinances and notices

III. Summary of enforcement of revised Pharmaceutical Affairs Law

A. Provisions enforced on July 30, 2003

1. Provisions related to biological products

(1) Designation of biological products and specified biological products

Biological products and specified biological products are classified based on the level of risk of infection of the product and designated.

(2) Standards for raw materials derived from living organisms

Based on Article 42 of the Pharmaceutical Affairs Law (with application *mutatis mutandis* in Article 68-5), the standards for raw materials derived from living organisms specify standards for handling of raw materials for biological products and all other drugs and medical devices manufactured using raw materials derived from living organisms, including fixed raw material selection criteria and treatment criteria in the manufacturing process.

(3) Retention and management of records

It is obligatory for the manufacturer, importer and distributor and in-country caretaker ("manufacturer, etc." hereinafter) to retain records related to the destination, product name, manufacturing number or code, date of transfer and shelf life of the biological product.

The retention time of records such as the transfer site by the manufacturer, etc. is a period not less than 30 years from the date of shipment for specified biological products and a period of not less than 10 years for biological products. In the case of biological products manufactured using human blood components, the period of retention is a period of not less than 30 years.

(4) Labeling

The immediate container or packaging will be labeled with "Biological" for biological products and with "Specified Biological" for specified biological products. The lettering for "Biological" and "Specified Biological" must be black letters with a black frame on a white background. The manufacturing number or code is also included in the label. Exemptions permitting adding an additional label to the older label are permitted within 2 years after enforcement.

(5) Package inserts

Before the name of the product, "Biological product" and "Specified biological product" must be added. If the product is a genetic recombinant, "recombinant" will be placed under the name. Guidelines have been established for entries in "Description" for biological products and for entries in "Initial precautions," "Description" and "Precautions" for specified biological products.

(6) Labeling of blood products

Specified biological products containing blood components will be labeled with the country of origin of the blood and method of blood collection (donated blood or non-donated blood) on the immediate container or packaging. The manufacturer, etc. will retain the documentation prepared confirming that the "blood was donated free of charge

voluntarily" based on the license certificate, etc. of the blood donation center in the donation region in accordance with GMP (GMPI) to verify that the blood was donated or non-donated.

(7) Periodic infection reports

Periodic infection reports have been introduced to call attention to integrated trends in infections of raw materials for which the direct effect on the product is still unclear and to facilitate understanding frequencies and trends from accumulated case reports. The items reported include the titles and summaries of reports on infections related to the raw material or the product, information on measures taken overseas, lists of infection reports for which a causal relation with the raw material or product can not be ruled out, amounts shipped and opinions on safety of the product by the manufacturer, etc.

(8) Manufacturing managers for biological products

Manufacturers and importers/distributors of biological products must employ manufacturing managers for biological products in addition to technical supervisors and import/distribution managers. Manufacturing managers for biological products must be a physician, a person with a degree in medicine specializing in microbiology or a person with a university degree in microbiology who has had at least three year's experience in the manufacture of biological products or other products requiring the same level of precautions in terms of public health and hygiene.

2. Adverse drug reaction reporting system by medical institutions

Cases of adverse reactions, defects or infections caused by the use of drugs or medical devices that are judged to require reporting in order to prevent the occurrence or spread of risks to public health or hygiene must be reported to the Minster of Health, Labor and Welfare. By applying the information collected from these reports, effective countermeasures can be drafted promptly and efficiently and fed back to medical institutions and companies.

3. Notification system for medical institution and investigator initiated clinical studies

Clinical research undertaken by medical institutions and physicians using unapproved drugs has been given the status of clinical trials. This step was intended to promote the use of results obtained in such research as approval application data for the drugs concerned and the rationalization of such research in compliance with regulations such as the GCP. When such medical institution and investigator initiated clinical studies are performed, it is specified that notifications must be submitted to the Minister of Health, Labor and Welfare.

4. Handling of drugs for which records must be kept

At present, records must be kept of the destination of certain drugs and manufacturing codes (lot numbers) by pharmacy proprietors as follows from the standpoint of rationalization of retention and management and rapid recalls. In the distribution stage, distributors are also obliged to keep records in some cases. However, since the range of drugs subject to safety measures such as recalls has widened, the range of drugs for which records must be kept has

expanded to cover all drugs. Since records of manufacturing number information results in a considerable burden in terms of clerical work, it is not obligatory at present.

B. Provisions to be enforced in 2005 (draft)

These provisions are currently mainly in draft form.

1. Date of enforcement

The date of enforcement of provisions to be enforced in 2005 is April 2005.

2. Business licenses

(1) Manufacturing businesses

a) Manufacturing/ distribution business licenses*

The manufacturing/ distribution business license is granted to an office that functions many as a manufacturer/ distributor. The license must be renewed every five years.

* These licenses are mainly for distributors who outsource up to 100% of manufacturing.

b) Granting of manufacturing/ distribution business licenses

Manufacturing/ distribution business licenses are granted by the prefectural governments.

c) Manufacturing/ distribution business license requirements and measures requiring compliance of manufacturers/ distributors

- Establishment of GVP and GPSP (ministerial ordinances)

The current Good Post-marketing Surveillance Practice (GPMSP) has been divided into the “Provisions concerning post-marketing safety measures such as collection and investigation of information on proper use and implementation of safety assurance measures by manufacturers and distributors” and “Provisions concerning studies and surveys performed by manufacturers and distributors after marketing.” The former are now called Good Vigilance Practice (GVP) that specifies licensing requirements and items for compliance by manufacturers/ distributors. The latter are now referred to as Good Post-marketing Surveillance Practice (GPSP).

- Establishment of GQP (ministerial ordinance)

Good Quality Practice (GQP) will be established to specify quality certification as a licensing requirement for manufacturers/ distributors.

- Provisions concerning the appointment of safety supervisors and quality certification supervisors will be specified in the GVP and GQP.

d) The duties, items for compliance and qualifications of general manufacturing and distribution supervisors will be specified.

(2) Manufacturing business

a) Manufacturing business licenses

Licenses for each product have been changed to licenses for each product category. These licenses will be granted by the Japanese government for businesses manufacturing biological products and radiopharmaceuticals, in vitro radioactive diagnostics or cell or tissue derived medical devices and by the prefectural authorities for other products. The licenses will be renewed every 5 years.

b) Manufacturing license requirements

The requirements to be met by manufacturing facilities are specified in structural and equipment standards for each license category.

c) Recognition of overseas manufacturing businesses

Overseas manufacturing plants with structure and facilities that comply with or exceed certain levels will be granted recognition as manufacturing business for each product category.

(3) Other businesses

a) Designated manufacturing and distribution businesses

The current in-country caretaker position will be abolished and the role of the in-country caretaker will be assumed by designated manufacturing/ distribution businesses designated by drug manufacturers/ distributors.

b) Pharmacy manufacturing/ distribution businesses

From the date of enforcement, pharmacy-manufacturing businesses will become pharmacy manufacturing/ distribution businesses. The license period will be 6 years and post-marketing safety management standards and manufacturing/ distribution quality certification standards will not be applied.

3. Approvals and regulatory affairs

(1) Approval-related revisions

To assure an approval review system that is in conformity with international levels, data attached to approval applications and approval contents have been revised to meet international standards such as ICH and GHTF (Global Harmonization Task Force).

(2) Revision related to minor changes in approved items

The range of changes in approved items that do not require a partial change (supplemental) approval application will be specified and a notification will be submitted within 30 days after the change.

(3) Regulations concerning registration of master files

Provisions in notifications concerning master files that can be registered, registration contents and changes will be coordinated.

(4) Conduct of GMP reviews

Products subject to GMP must undergo both paper and on-site GMP reviews or inspections for each approved product at the time of the approval review and within a period not exceeding 5 years after approval based on government ordinance. The GMP review is performed by the government for overseas plants and plants manufacturing new drugs, biological products, radiopharmaceuticals, new medical devices, medical devices derived from cells or tissues and class IV medical devices. GMP reviews will be conducted by the prefectural authorities for other plants. Review applications are submitted to the prefectural authorities for review conducted by both the government and the prefectures.

4. Radical revision of safety measures for medical devices

(1) Introduction of a classification system of medical devices based on risk

Designation of strictly controlled medical devices, controlled medical devices and ordinary medical devices.

(2) Establishment of basic requirements for medical devices and eligibility certification standards by the Minister of Health, Labor and Welfare. Designation of controlled medical devices not requiring approval and their standards

(3) Provisions concerning authorization and certification work by a registration certification institution

(4) Augmentation of requirements of distributors and leasers of strictly control medical devices

Preparation and retention of delivered product records, dissemination of information on proper use to consumers, and compliance with instructions of manufacturers and distributors when used devices are sold will be newly specified.

(5) Augmentation of safety measures for repairers

(6) Establishment of a ministerial ordinance on standards for non-clinical studies on the safety of medical devices (medical device GLP)

(7) Establishment of a ministerial ordinance on standards for clinical studies on medical devices (medical device GCP)

A system for conduct of clinical trials on medical devices, the same as the current system of clinical trials for drugs, will be established.

5. Others

(1) Certification

In keeping with the concept in the revised Pharmaceutical Affairs Law that “the responsibility of drug products on the market lies with the manufacturer/ distributor,” applicants for certification are “manufacturers/distributors.”

(2) Labeling

Because business status is changed from manufacturers to manufacturers/distributors in the revised Pharmaceutical Affairs Law, the responsibility for legally specified labeling

changes from manufacturers to manufacturers/distributors. The current labels will be considered as new labels for a period of 2 years from enforcement.

(3) Recalls

Recall reports will be issued by manufacturers/distributors.

(4) New Japanese term for prescription drugs

The current Japanese legal term “drugs requiring a prescription” will be abolished and changed to “type 1 drugs” although the English term prescription drugs remains unchanged.

(5) Provisions for persons acquiring special approvals

It has been specified that persons acquiring special approvals must take measures required to explain to and gain the understanding of the general public who purchase or use the products concerned indicating that reports must be submitted to the Minister of Health, Labor and Welfare concerning any adverse drug reactions suspected of being caused by the product concerned, that the results of use of the products must be surveyed and the survey results must be reported to the Minister, and that the products concerned are products subject to a special approval.

Appendix 2 “New” Drugs Recently Approved

12

7 New Drugs Approved and Notified by the Evaluation and Licensing Division of the Pharmaceutical and Medical Safety Bureau (PMSB), the Ministry of Health, Labour, and Welfare on October 16, 2003)

∇ (1) Telithromycin (Ketek tablets 300 mg, AVENTIS PHARMA JAPAN) ∇ (2) Insulin glulisine (genetical recombination) (Lantus injection cart 300 / kit 300, AVENTIS PHARMA JAPAN) ∇ (3) Pramipexole dihydrochloride monohydrate (Sifrol tablets 0.125 / 0.5 mg, NIPPON BOEHRINGER INGELHEIM)

∇ (4) Verteportin (Visudyne intravenous injection 15 mg, CIBA-GEIGY JAPAN) ∇ (5) Peginterferon Alfa-2a (Pegasys subcutaneous injection 90 / 180 μg, CHUGAI PHARMACEUTICAL) ∇ (6) Talaporfin Sodium (Laserphyrin, WAKO PURE CHEMICAL INDUSTRIES, Laserphyrin for injection 100 mg, MEIJI SEIKA)

∇ (7) Fosfluconazole (Prodif intravenous solution 100 / 200 / 400, PFIZER JAPAN)

11

2 New Drugs Approved and Notified by the Evaluation and Licensing Division of the Pharmaceutical and Medical Safety Bureau (PMSB), the Ministry of Health, Labour, and Welfare on July 17, 2003)

∇ (1) Pitavastatin calcium (pitavastatin calcium, NISSAN CHEMICAL, Livalo tablets 1 / 2 mg, KOWA) ∇ (2) Rizatriptan benzoate (Maxalt tablets 10 mg, Maxalt RPD tablets 10 mg, KYORIN PHARM)

10

3 New Drugs Approved and Notified by the Evaluation and Licensing Division of the Pharmaceutical and Medical Safety Bureau (PMSB), the Ministry of Health, Labour, and Welfare on April 16, 2003)

∇ (1) Sumatriptan (Imigran nasal spray 20, GLAXO SMITHKLINE) ∇ (2) Leflunomide (Arava tablets 10 / 20 / 100 mg, AVENTIS PHARMA JAPAN) ∇ (3) Capecitabine (Xeloda tablets 300, CHUGAI PHARMACEUTICAL)

9

2 New Drugs Approved and Notified by the Evaluation and Licensing Division of the Pharmaceutical and Medical Safety Bureau (PMSB), the Ministry of Health, Labour, and Welfare on January 31, 2003)

∇ (1) Azelnidipine (Calblock, UBE INDUSTRIES, Calblock tablets 8 / 16 mg, SANKYO) ∇ (2)

Sevelamer HCl (Renagel tablets 250, CHUGAI PHARMACEUTICAL, Phosblock tablets 250 mg, KIRIN BREWERY)

8

8 New Drugs Approved and Notified by the Evaluation and Licensing Division of the Pharmaceutical and Medical Safety Bureau (PMSB), the Ministry of Health, Labour, and Welfare on October 8, 2003)

∇ (1) Ferucarbotran (Resovist injection, NIHON SCHERING) ∇ (2) Esmolol HCl (Brevibloc injection 100 mg, MARUISHI PHARMACEUTICAL) ∇ (3) Prulifloxacin (Kisnon tablets 100, NIPPON SHINYAKU, Prulifloxacin JZ, JUZEN CHEMICAL, Sword tablets 100, MEIJI SEIKA)

∇ (4) Bacillus of Calmette and Guerin (BCG)･Connaught strain (Immucyst intravesical, NIPPON KAYAKU) ∇ (5) Ivermectin (Stromectol tablets 3 mg, BANYU PHARMACEUTICAL) ∇ (6) Micafungin sodium (Funguard for injection 50 / 75 mg, FUJISAWA PHARMACEUTICAL)

∇ (7) Telmisartan (Micardis capsules 20 / 40 mg, NIPPON BOEHRINGER INGELHEIM) ∇ (8) Brinzolamide (Azopt ophthalmic suspension 1%, ALCON JAPAN)

7

4 New Drugs Approved and Notified by the Evaluation and Licensing Division of the Pharmaceutical and Medical Safety Bureau (PMSB), the Ministry of Health, Labour, and Welfare on July 5, 2002)

∇ (1) Landiolol HCl (Landiolol HCl TKS, NAGASE ChemteX, Onoact for injection 50, ONO PHARMACEUTICAL) ∇ (2) Loratadine (Loratadine bulk, Claritin tablets 10 mg, SCHERING-PLOUGH) ∇ (3) Exemestane (Aromasin tablets 25 mg, PHARMACIA)

∇ (4) Gefitinib (Iressa tablets 250, ASTRA ZENECA)

6

6 New Drugs Approved and Notified by the Evaluation and Licensing Division of the Pharmaceutical and Medical Safety Bureau (PMSB), the Ministry of Health, Labour, and Welfare on April 11, 2002)

∇ (1) Gatifloxacin hydrate (Gatiflo tablets 100 mg, KYORIN PHARMACEUTICAL) ∇ (2) Amrubicin HCl (Calsed bulk, Calsed injection 20 / 50 mg, SUMITOMO CHEMICAL, SUMITOMO PHARMACEUTICAL) ∇ (3) Pazufloxacin mesilate (Pasil M, TOYAMA CHEMICAL, Pazucross injection 300, MITSUBISHI PHARMA)

∇ (4) Salmeterol xinafoate (Serevent inhalor 25, Serevent Rotadisk 25 / 50, GLAXO SMITHKLINE) ∇ (5) Sivelestat sodium hydrate (Elaspol injection 100, ONO PHARMACEUTICAL, sivelestat sodium hydrate SFL, SHIONO FINESSE) ∇ (6) Eletriptan hydrobromide (Lelpax tablets 20 mg, PFIZER)

5

14 New Drugs Approved and Notified by the Evaluation and Licensing Division of the Pharmaceutical and Medical Safety Bureau (PMSB), the Ministry of Health, Labour, and

Welfare on April 27, 2001)

∇ (1) Quinupristin-dalfopristin (Synercid injection, AVENTIS PHARMA JAPAN) ∇ (2) infliximab (recombinant) (Remicade injection 100, TANABE PHARMACEUTICALS) ∇ (3) Somatropin (growth hormone human), (Genotropin 1.3 mg, Genotropin KabiQuick 0.7 mg / 1.3 mg, PHARMACIA)

∇ (4) Imidapril hydrochloride (Tanatril tablets, TANABE PHARMACEUTICAL) ∇ (5) basiliximab (recombinant) (Simulect injection 20 mg, CIBA GEIGY) ∇ (6) Cladribine (Leustatin injection 8 mg, JANSSEN PHARMACEUTICAL)

∇ (7) Diclofenac sodium (Naboal SR capsules 37.5, SSP, Voltaren SR Capsules 25, DOJIN IYUAKU KAKO) ∇(8) Goserelin acetate (Zoladex LA 10.8 mg depot, ASTRA ZENECA)

∇(9) Risedronate sodium hydrate (Risedronate bulk, AJINOMOTO PHARMA) ∇(10) Risedronate sodium hydrate (Actonel tablets 2.5 mg, AJINOMOTO PHARMA) ∇ (11) Risedronic acid (Benet tablets 2.5 mg, TAKEDA CHEMICAL INDUSTRIES)

∇ (12) Palivizumab (Synagis IM injection 50 mg / 100 mg, DAINABOT) ∇ (13) Seltamivir phosphate (Tamiflu drysyrup 3%, NIPPON ROCHE)

4

1 New Drug Approved and Notified by the Evaluation and Licensing Division of the Pharmaceutical and Medical Safety Bureau (PMSB), the Ministry of Health, Labour, and Welfare on December 13, 2001)

∇ (1) Azithromycin hydrate (Zithromac tablets 600 mg, PFIZER PHARMACEUTICALS)

3

3 New Drugs Approved and Notified by the Evaluation and Licensing Division of the Pharmaceutical and Medical Safety Bureau (PMSB), the Ministry of Health, Labour, and Welfare on Novemberl 21, 2001)

∇ (1) Ribavirin (Rebetol capsules 200 mg, SCHERING-PLOUGH) ∇ (2) Interferon alfa (Intron-A, SCHERING-PLOUGH) ∇ (3) Imatinib mesilate (Glivec capsules, CIBA GEIGY)

2

9 New Drugs Approved and Notified by the Evaluation and Licensing Division of the Pharmaceutical and Medical Safety Bureau (PMSB), the Ministry of Health, Labour, and Welfare on October 2, 2001)

∇ (1) Ethaneperoxoic acid (Stock solution, Aceside disinfectant 6%, SARAYA) ∇ (2) Fluticasone propionate (Flutide 50 / 100 Diskus, Flutide 50/100 Rotadisk, GLAXO

SMITHKLINE) ∇ (3) Insulin (Insulin asparto, NovoRapid 150, NovoRapid FlexPen 300, NovoRapid 100 u/mL vials, NovoRapid 300, NOVO NORDISK PHARMA)

∇ (4) Fudosteine (Fudosteine Dojin, DOJIN IYUAKU KAKO; Fudosteine Yuki, YUKIGOSEI KOGYO; Fudosteine, Spelear tablets 200, SSP; Cleanal tablets 200; MITSUBISHI PHARMA) ∇ (5) Interferon-alfacon-1 (Advaferon stock solution, Advaferon Inj 1200 / 1800, YAMANOUCHI PHARMACEUTICAL; Infagen Inj 1200 / 1800, AMGEN)

∇ (6) Fentanyl (Durotep patch 2.5 mg / 5 mg / 7.5 mg / 10 mg, JANSSEN PHARMACEUTICAL, Durotep patch Kyowa 2.5 mg / 5 mg / 7.5 mg / 10 mg, KYOWA HAKKO KOGYO) ∇ (7) Biapenem（Omegacin iv drip infusion 0.3 g / 0.3 g bags, Omegacin skin test, WYETH LEDERLE JAPAN; Omegacin iv drip infusion 0.3 g bags, HISHIYAMA PHARMACEUICAL, Biapenem Kaneka, KANEKA） ∇ (8) Orthophthalaldehyde (JOHNSON & JOHNSON) ∇ (9) Phtharal (DISOPA Solution0.55%, JOHNSON & JOHNSON)

1

14 New Drugs Approved and Notified by the Evaluation and Licensing Division of the Pharmaceutical and Medical Safety Bureau (PMSB), the Ministry of Health, Labour, and Welfare on April 27, 2001)

∇ (1) Bunazosin hydrochloride (Detantol 0.01 % Ophthalmic Solution, SANTEN PHARMACEUTICAL) ∇ (2) Insulin lispro (genetical recombination) (Humalog vials 100, kits, and carts, genetically produced insulin lispro, ELI LILLY JAPAN) ∇ (3) Cevimeline hydrochloride hydrate (Saligren 30-mg capsules, NIPPON KAYAKU)

∇ (4) Tacrolimus hydrate (Prograf 0.5 / 1 / 5-mg capsules, 5-mg injection, 0.2/1-mg granules, FUJISAWA PHARMACEUTICAL) ∇ (5) Ciclosporin (Sandimmun injection/oral solution, 25/50-mg capsules, Neoral oral solution, 10 / 25 / 50-mg capsules, CIBA GEIGY)

∇ (6) Azathioprine (Imuran tablets, GLAXOSMITHKLINE; Azanin tablets, TANABE SEIYAKU) [Second Drug Committee, May 9, 2001] ∇ (7) Rituximab（genetical recombination (Rituxan 10-mg/mL injection, ZENYAKU KOGYO) ∇ (8) Alendronate sodium hyrate (Fosamc 5-mg tablets, BANYU PHARMACEUTICAL; Bonalon 5-mg tablets, TEIJIN) ∇ (9) Maxacalcitol (Oxarol ointment, CHUGAI PHARMACEUTICAL)

∇ (10) Montelukast sodium (Singulair 10-mg tablets, Singulair 5-mg chewable tablets, BANYU PHARMACEUTICAL; Kipres 10-mg tablets, Kipres 5-mg chewable tablets, KYORIN PHARMACEUTICAL) ∇ (11) Suplatast tosilate (IPD 5% dry syrup, TAIHO PHARMACEUTICAL) ∇ (12) Zolmitriptan (Zomig 2.5-mg tablets, ASTRA ZENECA) ∇ (13) Sumatriptan succinate (Imigran 50-mg tablets, GLAXO WELLCOME) ∇ (14) Botulinum toxin type A (Botox injection, ALLERGAN)

Appendix 3 Important Notifications and Ordinances Related to Biological Products

Important Notificiations Issued in Relation to Drugs and Medical Devices Manufactured Using Materials of Human or Animal Origin and Cell or Tissue-Derived Components		
1.	Complete Recall of Dried Human Dura	Medical Devices Div, PAB, Notification No. 108 dated May 21, 1997
2.	Complete Recall of Dried Human Dura	Inspection & Guidance Div, PAB, Notification No. 78 dated May 21, 1997
3.	Quality and Safety Assurance of Cell/Tissue Pharmaceuticals and Cell/Tissue-Derived Medical Devices	PMSB, Notification No. 906 dated July 30, 1999
4.	Quality and Safety Assurance of Drugs Manufactured Using Human or Animal-Derived Components as Raw Materials	PMSB, Notification No. 1314 dated Decemberr 26, 2000
5.	Approval Applications for Quality and Safety Assurance of Drugs Manufactured Using Human or Animal-Derived Components as Raw Materials	Evaluation and Licensing Div, PMSB, Notification No. 1807 dated December 26, 2000
6.	Import of Drugs Manufactured Using Human or Animal (Including Bovine)-Derived Components as Raw Materials　ヒト又は動物（ウシ等を含む）由来物を原料として製造される医薬品等の輸入の取扱いについて	PMSB, Notification No. 127 dated February 23, 2001 2001年2月23日、医薬発第127号
7.	Enforcement of MHLW Ordinance on Amended Pharmaceutical Affairs Law Enforcement Regulations (Handling of Cell/Tissue-Derived Pharmaceuticals and Medical Devices)	PMSB, Notification No. 266 dated March 28, 2001
8.	Enforcement of Ethical Guidelines for Institutions Undertaking Human Genome and Gene Analysis	HPB, Notification No. 390 dated April 2, 2001
9.	Applications for Partial Changes in Approved Items with Respect to Quality and Safety Assurance of Drugs Manufactured Using Human or Animal-Derived Components as Ingredients	Evaluation and Licensing Div, PMSB, Notification No. 1046 dated July 10, 2001
10.	License Applications for Selling (Importing) Cell/Tissue-Derived Medical Devices	Evaluation and Licensing Div, PMSB, Notification No. 1283 dated August 21, 2001
11.	Guideline for Establishment and Use of Human ES Cells	Ministry of Education, Culture, Sports, Science and Technology, Notification No. 155 dated September 25, 2001
12.	Import of Drugs and Medical Devices Manufactured Using Human or Animal (Including Bovine)-Derived Components as Raw Materials	PMSB, Notification No. 1073 dated October 2, 2001
13.	Virus checking, etc. in Applications for Partial Changes in Approved Items for Quality and Safety Assurance of Drugs or Medical Devices Manufactured Using Human or Animal-Derived Components as Raw Materials	Evaluation and Licensing Div, PMSB, Notification No. 1552 dated November 26, 2001
14.	Quality and Safety Assurance of Drugs Manufactured Using Human or Animal-Derived	Evaluation and Licensing Div, PMSB, Notification No. 0226001 dated

	Components as Raw Materials	February 26, 2002
15.	Applications for Partial Changes in Approved Items for Quality and Safety Assurance of Drugs or Medical Devices Manufactured Using Human or Animal-Derived Components as Raw Materials	Evaluation and Licensing Div, PMSB, Notification No. 0320008 dated March 20, 2002
16.	Quality and Safety Assurance of Drugs Manufactured Using Human or Animal-Derived Components as Raw Materials	PMSB, Notification No. 0521001 dated May 21, 2002
17.	Handling of Drugs, Medical Devices, Quasi-medicinal Products and Cosmetics Manufactured Using Human or Animal-Derived Components as Raw Materials	PMSB, Notification No. 0731010 dated July 31, 2002
18.	Approval Applications for Drugs Manufactured Using Human or Animal-Derived Components as Raw Materials	Evaluation and Licensing Div, PMSB, Notification No. 0823001 dated August 23, 2002

Important Notificiations Issued in Relation to Bovine-Derived Components		
1.	Bovine Materials of British Origin for Pharmaceutical Use	Evaluation and Licensing Div, PAB, Notification No. 177 dated March 28, 1996
2.	Handling of Bovine Materials for Pharmaceutical Use	Evaluation and Licensing Div, PAB, Notification No. 207 dated April 10, 1996
3.	Handling of Ruminant-Derived Materials for Pharmaceutical Use	Research and Development Div, PAB, Notification No. 13 dated April 17, 1996
4.	Quality and Safety Assurance of Drugs Manufactured Using Bovine-Derived Components as Raw Materials	PMSB, Notification No. 1226 dated December 12, 2000
5.	Approval Applications for Quality and Safety Assurance of Drugs Manufactured Using Bovine-Derived Components as Raw Materials	Evaluation and Licensing Div, PMSB, Notification No. 1293 dated December 12, 2000
6.	Local Approval Applications for Quality and Safety Assurance of Drugs and Quasi-drugs Manufactured Using Bovine-Derived Components as Raw Materials (Notification)	PMSB, Notification No. 946 dated January 15, 2001
7.	Applications for Partial Changes in Approved Items of Drugs Manufactured Using Bovine-Derived Components as Raw Materials	Evaluation and Licensing Div, PMSB, Notification No. 63 dated January 26, 2001
8.	Quality and Safety Assurance of Drugs Manufactured Using Bovine-Derived Components as Raw Materials	PMSB, Notification No. 438 dated April 24, 2001
9.	Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Components of Domestic Bovine Origin Raw Materials	PMSB, Notification No. 906 dated September 19, 2001
10.	Approval Applications for Strengthening of Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Bovine-Derived Components as Raw Materials	Evaluation and Licensing Div, PMSB, Notification No. 1434 dated October 16, 2001
11.	Voluntary Recall of Drugs and Medical Devices	Inspection and Guidance Div, PMSB,

	Manufactured Using Bovine-Derived Components as Raw Materials	Notification No. 1131 dated October 31, 2001
12.	Voluntary Recall of Drugs and Medical Devices Manufactured Using Bovine-Derived Components as Raw Materials	Evaluation and Licensing Div, PMSB, Notification No. 1465 dated October 31, 2001
13.	Voluntary Recall of Drugs and Medical Devices Manufactured Using Bovine-Derived Components as Raw Materials	Safety Div, PMSB, Notification No. 148 dated October 31, 2001
14.	Handling of Approval Applications for Strengthening Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Bovine-Derived Components Raw Materials	Evaluation and Licensing Div, PMSB, Notification No. 1471 dated November 1, 2001
15.	Strengthening of Quality and Safety Assurance of Drugs, Medical Devices, etc., Manufactured Using Bovine-Derived Materials as Raw Materials	PMSB, Notification No. 0827002 dated August 27, 2002
16.	Strengthening of Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Components of Human or Animal Origin as Raw Materials	PMSB, Notification No. 0414004 dated April 14, 2003
17.	Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Components of Canadian Bovine Origin as Raw Materials	PMSB, Notification No. 0522002 dated May 22, 2003
18.	Handling of Approval Applications for Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Components of Canadian Bovine Origin as Raw Materials	Evaluation and Licensing Div, PMSB, Notification No. 0605001 dated June 5, 2003
19.	Strengthening of Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Human- or Bovine-derived Components as Raw Materials	Blood and Blood Products Div, PFSB, Notification No. 0725002 dated July 25, 2003 and Evaluation and Licensing Div, PFSB, Notification No. 0725001 dated July 25, 2003
20.	Q and A on Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Components of Canadian Bovine Origin as Raw Materials	Notification dated August 1, 2003
21.	Risk Assessment Criteria for License Applications for Partial Changes in Approved Items of Drugs and Medical Devices Manufactured Using Bovine-Derived Components as Raw Materials	Safety Div, PFSB, Notification No. 0801001 dated August 1, 2003, Evaluation and Licensing Div, PFSB, Notification No. 0801001 dated August 1, 2003

Important Notificiations Issued in Relation to Biological Products		
1.	Information to be Contained in Labeling and Package Inserts of Biological Products	PMSB, Notification No. 0515005 dated May 15, 2003
2.	Periodical Infection Reporting System for Biological Products	PMSB, Notification No. 0515008 dated May 15, 2003
3.	Information for Users of Specified Biological Products and Records and Storage of Specific Biological Products	PMSB, Notification No. 0515012 dated May 15, 2003
4.	Information for Users of Specified Biological Products and Records and Storage of	PMSB, Notification No. 0515011 dated May 15, 2003

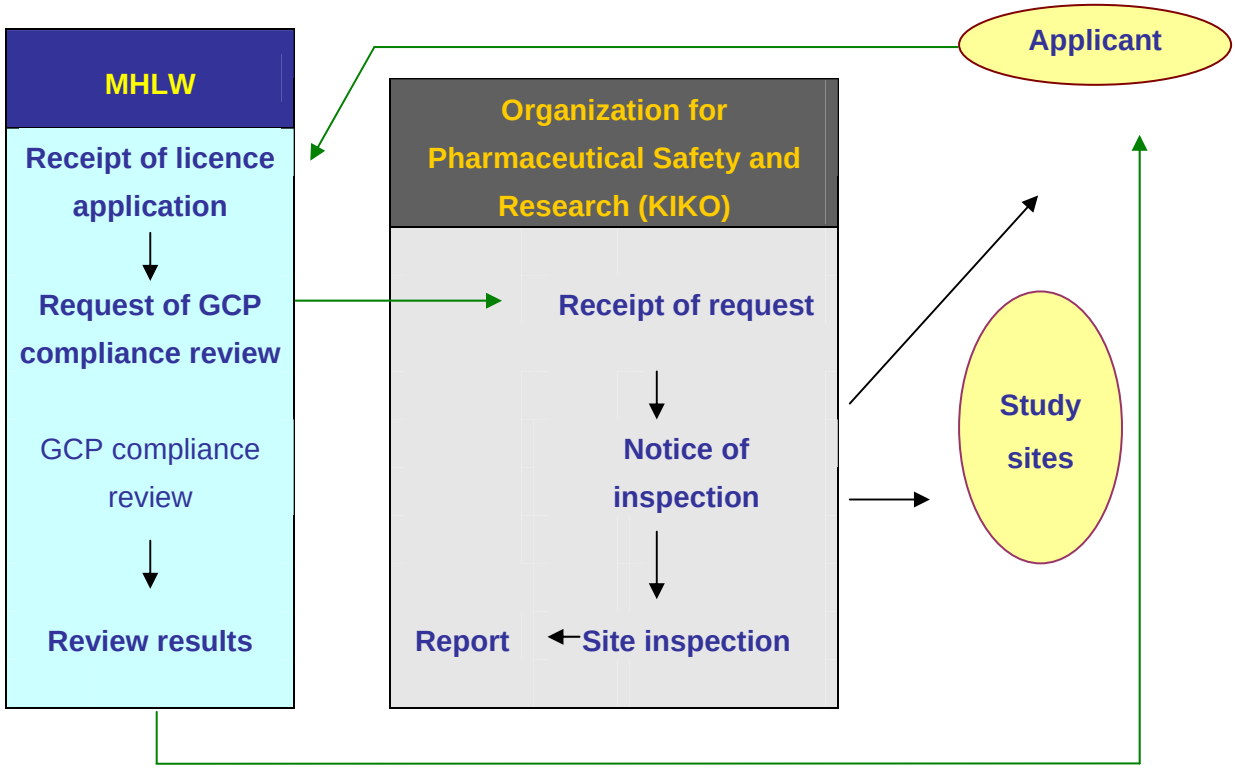
	Designated Biological Products	
5.	Biological Products and Specified Biological Products Designated by the Minister of the MHLW	MHLW, Notification No. 209 dated May 20, 2003
6.	Enforcement of Ministerial Ordinance to Partially Amend Manufacturing Control and Quality Control Regulations for Drugs and Quasi-Drugs (Handling of Biological Products)	PMSB, Notification No. 0520004 dated May 20, 2003
7.	Biological Products and Specified Biological Products	Notification dated May 20, 2003
8.	Items to be Listed in Package Inserts of Biological Products	Safety Div, PMSB, Notification No. 0520004 dated May 20, 2003
9.	Designation of Biological Products and Specified Biological Products and Establishment of Standards of Biological Materials for Pharmaceutical Use	PMSB, Notification No. 0520001 dated May 20, 2003
10.	Standards of Biological Materials for Pharmaceutical Use	MHLW, Notification No. 210 dated May 20, 2003
11.	Handling of Records on Specified Biological Products at the Time of Closure of Medical Institutions	PMSB, Notification No. 0618009 dated June 18, 2003
12.	Methods of Surveys and Entries in Periodic Reports of Infections due to Biological Products	Safety Div, PMSB, Notification No. 0618001 dated June 18, 2003
13	Q and A on Information for Users of Specified Biological Products and Records and Storage of Specified Biological Products	Blood and Blood Products Div, Notification No. 0702001 dated July 2, 2003, and Safety Div, PFSB, Notification No. 0702001 dated July 2, 2003
14.	Applications for the Approval of Outsourcing of Recording and Storage of Specified Biological Products	Safety Div, PFSB, Notification No. 0730001 dated July 30, 2003
15.	Q and A on Handling Biological Products by the Manufacturing (Import) Manager	Notification dated August 20, 2003

Appendix 4 Records of GCP inspection

	April 1, 1997 – March 31, 1998	April 1, 1998 – March 31, 1999	April 1, 1999 – March 31, 2000	April 1, 2000 – March 31, 2001
Number of drug substances inspected	17	39	69	47
Number of products inspected	40	79	159	109

	April 1, 2001 – March 31, 2002	April 1, 2002 – March 31, 2003	April 1, 2003 – November 30, 2003	
Number of drug substances inspected	63	47	40	
Number of products inspected	119	89	82	

Flowsheet of GCP Inspection at Site



Appendix 5 Education of Medical Representatives (MR)

The education and training of medical representatives (MR) in Japan has been undertaken since 1979 based on the guidelines for education and training of medical representatives, which are applied in a voluntary manner based on a consensus within the pharmaceutical industry.

Social pressures demanded an objective evaluation of the minimum knowledge required for MR and an MR accreditation system was introduced to improve the quality of MR. In 1996, the Japan MR Education center was set up as a preliminary organization, and in 1997, the MR Education & Accreditation Center of Japan (MR-EAJC) was established as a non-profit organization authorized by the MHW.

In October 2000, this Center established new guidelines for education and training of medical representatives (the Guidelines) for MR education in the 21st century in consideration of the introduction of the MR accreditation system, progress in medicine and changes in social conditions.

Education and training of MR in Japan is now based on these Guidelines. They can be summarized as follows.

1. Definition of MR

Medical representative (MR) refers to a person whose main task is to present, collect and disseminate information related to the quality, efficacy and safety of drugs by means of direct talks with health professionals in order to promote the proper use of prescription drugs.

2. Implementation of education and training

Education and training is performed on the basis of the guidelines under the responsibility of the company. The companies may outsource education and training of MR to educational and training facilities authorized by the MR-EAJC.

3. System of education and training

Education and training of MR consists of introductory courses and continuing education courses.

4. Introductory course

The introductory course is intended to provide qualifications required of MR.

1) Subjects

Persons intending to become MR.

2) Curriculum

Subjects		Hours of training
Basic training	General medicine (general medicine, medical ethics and regulatory system)	At least 70 hours
	Diseases and treatment	At least 130 hours
	Pharmacology	At least 30 hours
	Pharmaceutics	At least 30 hours
	Package inserts	At least 20 hours
	PMS	At least 20 hours
Practical training	Practical skills	At least 150 hours
	Knowledge of products	Dependent on company's program
	Other training	

Physicians, dentists and pharmacists who have the respective national qualifications are exempted from basic training on diseases and treatment, pharmacology and pharmaceutics.

3) Text

For basic training, the "MR Training Text" produced by the MR-EAJC is used as the main text.

5. Continuing education

Continuing education is intended to maintain and improve the qualifications required of MR. After completion of the introductory course, scheduled continuing education is provided every year as lifetime education.

1) Subjects

MR who have completed the introductory course and continuing education

2) Curriculum

Subjects		Hours of training
Basic training	Ethics	At least 10 hours
	General overview, regulatory affairs and systems for drugs	At least 10 hours

	Diseases and treatment, pharmacology and pharmaceutics	At least 10 hours
	PMS	At least 10 hours
Practical training	Practical skills	Dependent on company's program
	Knowledge of products	

6. Intracompany system for education and training

Companies must designate supervisors in charge of education and training and managers to undertake such education and training. They shall be registered by the MR-EAJC.

7. Recognition of education and training

When companies undertake education and training, it must be recognized by the MR-EAJC. Persons who have completed the introductory course shall be eligible to take the MR accreditation examination. MR who have passed the MR accreditation examination shall be able to renew their MR accreditation after completion of five consecutive years of continuing basic education. System for education and training of medical representatives (MR)

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APPENDIX

Japanese Pharmaceutical Regulations and Adrministration

March 2003

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