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)

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

<table>
<thead>
<tr>
<th>Appendix</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix 1</td>
<td>REVISION OF PHARMACEUTICAL SYSTEM</td>
<td>1</td>
</tr>
<tr>
<td>Appendix 2</td>
<td>“NEW” DRUGS RECENTLY APPROVED</td>
<td>12</td>
</tr>
<tr>
<td>Appendix 3</td>
<td>IMPORTANT NOTIFICATIONS AND ORDINANCES RELATED TO BIOLOGICAL PRODUCTS</td>
<td>16</td>
</tr>
<tr>
<td>Appendix 4</td>
<td>RECORDS OF GCP INSPECTION</td>
<td>20</td>
</tr>
<tr>
<td>Appendix 5</td>
<td>EDUCATION OF MEDICAL REPRESENTATIVES (MR)</td>
<td>21</td>
</tr>
</tbody>
</table>
Appendix 1   Revision of Pharmaceutical System

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

<table>
<thead>
<tr>
<th>General explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Revision of the Pharmaceutical Affairs Law</td>
</tr>
</tbody>
</table>

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.


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

<table>
<thead>
<tr>
<th>I. Government ordinances and notices based on revisions of the pharmaceutical system</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 public comment from June to August 2003 and many opinions were submitted. At present, work related to enforcement is underway.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Revision of other laws and ordinances related to revision of the Pharmaceutical Affairs Law</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
<tr>
<td>- Related laws and ordinance enforced on July 30, 2003</td>
</tr>
<tr>
<td>(1) Pharmaceutical Affairs Law Enforcement Ordinance (export exemptions and exemptions for drugs granted special licenses before approval)</td>
</tr>
<tr>
<td>(2) Pharmaceutical Affairs Law Enforcement Regulations (biological products, ADR reports from medical institutions, medical institution and investigator initiated clinical trials)</td>
</tr>
<tr>
<td>(3) Revision of other ministerial ordinances</td>
</tr>
<tr>
<td>a) Ordinance on standards for conduct of medical institution and investigator initiated clinical trials (partial revision of current GCP ordinance)</td>
</tr>
<tr>
<td>b) Structural and equipment regulations for pharmacies, etc. (provisions related to manufacturing plants for specified biological products)</td>
</tr>
<tr>
<td>c) Manufacturing control and quality control regulations for drugs and medical devices (GMP) (retention of manufacturing records)</td>
</tr>
<tr>
<td>(4) Newly issued and revised notices</td>
</tr>
<tr>
<td>a) System for designation of biological products and specified biological products</td>
</tr>
<tr>
<td>b) Establishment of standards for raw materials derived from living organisms (Article 42 of the Pharmaceutical Affairs Law)</td>
</tr>
</tbody>
</table>
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

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) Talaporfín Sodium (Laserphyrin, WAKO PURE CHEMICAL INDUSTRIES, Laserphyrin for injection 100 mg, MEIJI SEIKA)
∇ (7) Fosfluconazole (Prodif intravenous solution 100 / 200 / 400, PFIZER JAPAN)

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)

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)

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 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)

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, Onoaact 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 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) Amrubinic 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)

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
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 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 November 21, 2001

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

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

<table>
<thead>
<tr>
<th>Important Notifications Issued in Relation to Drugs and Medical Devices Manufactured Using Materials of Human or Animal Origin and Cell or Tissue-Derived Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
</tr>
<tr>
<td>4.</td>
</tr>
<tr>
<td>7.</td>
</tr>
<tr>
<td>12.</td>
</tr>
<tr>
<td>13.</td>
</tr>
</tbody>
</table>
### Important Notifications Issued in Relation to Bovine-Derived Components

<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
<th>Issuing Authority</th>
<th>Notification No.</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>Handling of Bovine Materials for Pharmaceutical Use</td>
<td>Evaluation and Licensing Div, PAB</td>
<td>207</td>
<td>April 10, 1996</td>
</tr>
<tr>
<td>3.</td>
<td>Handling of Ruminant-Derived Materials for Pharmaceutical Use</td>
<td>Research and Development Div, PAB</td>
<td>13</td>
<td>April 17, 1996</td>
</tr>
<tr>
<td>11.</td>
<td>Voluntary Recall of Drugs and Medical Devices</td>
<td>Inspection and Guidance Div, PMSB</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Important Notifications Issued in Relation to Biological Products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Information to be Contained in Labeling and Package Inserts of Biological Products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Periodical Infection Reporting System for Biological Products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Information for Users of Specified Biological Products and Records and Storage of Specific Biological Products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Information for Users of Specified Biological Products and Records and Storage of</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Manufactured Using Bovine-Derived Components as Raw Materials**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>12.</td>
<td>Voluntary Recall of Drugs and Medical Devices Manufactured Using Bovine-Derived Components as Raw Materials</td>
</tr>
<tr>
<td>13.</td>
<td>Voluntary Recall of Drugs and Medical Devices Manufactured Using Bovine-Derived Components as Raw Materials</td>
</tr>
<tr>
<td>14.</td>
<td>Handling of Approval Applications for Strengthening Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Bovine-Derived Components Raw Materials</td>
</tr>
<tr>
<td>15.</td>
<td>Strengthening of Quality and Safety Assurance of Drugs, Medical Devices, etc., Manufactured Using Bovine-Derived Materials as Raw Materials</td>
</tr>
<tr>
<td>16.</td>
<td>Strengthening of Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Components of Human or Animal Origin as Raw Materials</td>
</tr>
<tr>
<td>17.</td>
<td>Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Components of Canadian Bovine Origin as Raw Materials</td>
</tr>
<tr>
<td>18.</td>
<td>Handling of Approval Applications for Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Components of Canadian Bovine Origin as Raw Materials</td>
</tr>
<tr>
<td>19.</td>
<td>Strengthening of Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Human- or Bovine-derived Components as Raw Materials</td>
</tr>
<tr>
<td>20.</td>
<td>Q and A on Quality and Safety Assurance of Drugs and Medical Devices Manufactured Using Components of Canadian Bovine Origin as Raw Materials</td>
</tr>
<tr>
<td>21.</td>
<td>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</td>
</tr>
</tbody>
</table>

**Notification No. 1131 dated October 31, 2001**

**Evaluation and Licensing Div, PMSB, Notification No. 1465 dated October 31, 2001**

**Safety Div, PMSB, Notification No. 148 dated October 31, 2001**

**Evaluation and Licensing Div, PMSB, Notification No. 1471 dated November 1, 2001**

**PMSB, Notification No. 0827002 dated August 27, 2002**

**PMSB, Notification No. 0414004 dated April 14, 2003**

**PMSB, Notification No. 0522002 dated May 22, 2003**

**Evaluation and Licensing Div, PMSB, Notification No. 0605001 dated June 5, 2003**


**Notification dated August 1, 2003**

**Safety Div, PFSB, Notification No. 0801001 dated August 1, 2003, Evaluation and Licensing Div, PFSB, Notification No. 0801001 dated August 1, 2003**

**PMSB, Notification No. 0515005 dated May 15, 2003**

**PMSB, Notification No. 0515008 dated May 15, 2003**

**PMSB, Notification No. 0515012 dated May 15, 2003**

**PMSB, Notification No. 0515011 dated May 15, 2003**
### Designated Biological Products

<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
<th>Notification</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.</td>
<td>Biological Products and Specified Biological Products Designated by the Minister of the MHLW</td>
<td>MHLW, Notification No. 209 dated May 20, 2003</td>
</tr>
<tr>
<td>6.</td>
<td>Enforcement of Ministerial Ordinance to Partially Amend Manufacturing Control and Quality Control Regulations for Drugs and Quasi-Drugs (Handling of Biological Products)</td>
<td>PMSB, Notification No. 0520004 dated May 20, 2003</td>
</tr>
<tr>
<td>8.</td>
<td>Items to be Listed in Package Inserts of Biological Products</td>
<td>Safety Div, PMSB, Notification No. 0520004 dated May 20, 2003</td>
</tr>
<tr>
<td>11.</td>
<td>Handling of Records on Specified Biological Products at the Time of Closure of Medical Institutions</td>
<td>PMSB, Notification No. 0618009 dated June 18, 2003</td>
</tr>
<tr>
<td>15.</td>
<td>Q and A on Handling Biological Products by the Manufacturing (Import) Manager</td>
<td>Notification dated August 20, 2003</td>
</tr>
</tbody>
</table>
### Appendix 4  
**Records of GCP inspection**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of drug substances inspected</strong></td>
<td>17</td>
<td>39</td>
<td>69</td>
<td>47</td>
</tr>
<tr>
<td><strong>Number of products inspected</strong></td>
<td>40</td>
<td>79</td>
<td>159</td>
<td>109</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of drug substances inspected</strong></td>
<td>63</td>
<td>47</td>
<td>40</td>
</tr>
<tr>
<td><strong>Number of products inspected</strong></td>
<td>119</td>
<td>89</td>
<td>82</td>
</tr>
</tbody>
</table>

**Flowsheet of GCP Inspection at Site**

1. **Receipt of licence application**
2. **Request of GCP compliance review**
3. **GCP compliance review**
4. **Review results**
5. **Organization for Pharmaceutical Safety and Research (KIKO)**
6. **Receipt of request**
7. **Notice of inspection**
8. **Report Site inspection**
9. **Study sites**
10. **MHLW**
11. **Applicant**
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
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

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Hours of training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic training</td>
<td></td>
</tr>
<tr>
<td>Ethics</td>
<td>At least 10 hours</td>
</tr>
<tr>
<td>General overview, regulatory</td>
<td></td>
</tr>
<tr>
<td>affairs and systems for drugs</td>
<td>At least 10 hours</td>
</tr>
</tbody>
</table>
### Diseases and treatment, pharmacology and pharmaceutics
- **At least 10 hours**

### PMS
- **At least 10 hours**

### Practical training

<table>
<thead>
<tr>
<th>Practical skills</th>
<th>Knowledge of products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dependent on company’s program</strong></td>
<td></td>
</tr>
</tbody>
</table>

---

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)
Editors (in the order of chapter in responsible)

<table>
<thead>
<tr>
<th>Chapter 1</th>
<th><a href="mailto:kurusu.katsunori@me.m-pharma.co.jp">kurusu.katsunori@me.m-pharma.co.jp</a>, Mitsubishi Welfarma</th>
<th>KURISU, Katsunori</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 2</td>
<td><a href="mailto:y2-yamamoto@hhc.eisai.co.jp">y2-yamamoto@hhc.eisai.co.jp</a>, Eisai</td>
<td>YAMAMOTO, Yukio</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:Sakaiya_Kenji@takeda.co.jp">Sakaiya_Kenji@takeda.co.jp</a>, Takeda Chemical Industries</td>
<td>SAKAIYA, Kenji</td>
</tr>
<tr>
<td>Chapter 3</td>
<td><a href="mailto:Kondo4a@daiichipharm.co.jp">Kondo4a@daiichipharm.co.jp</a>, Daiichi Pharmaceutical</td>
<td>KONDO, Masaki</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:higuchimsy@chugai-pharm.co.jp">higuchimsy@chugai-pharm.co.jp</a>, Chugai Pharmaceutical</td>
<td>HIGUCHI, Masayoshi</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:minony@banyu.co.jp">minony@banyu.co.jp</a>, Banyu Pharmaceutical</td>
<td>MINO, Nobuyuki</td>
</tr>
<tr>
<td>Chapter 4</td>
<td><a href="mailto:hiroyuki.satou@shionogi.co.jp">hiroyuki.satou@shionogi.co.jp</a>, Shionogi Pharmaceutical</td>
<td>SATOU, Hiroyuki</td>
</tr>
<tr>
<td>Chapter 5</td>
<td><a href="mailto:matsushita@kyowa.co.jp">matsushita@kyowa.co.jp</a>, Kyowa Hakko Kogyo</td>
<td>MATSUSHITA, Kiyoshi</td>
</tr>
<tr>
<td>Chapter 6</td>
<td><a href="mailto:satoto@tky.otsuka.co.jp">satoto@tky.otsuka.co.jp</a>, Otsuka Pharmaceutical</td>
<td>SATO, Toshio</td>
</tr>
<tr>
<td>Coordination</td>
<td><a href="mailto:hiroyuki_arai@po.fujisawa.co.jp">hiroyuki_arai@po.fujisawa.co.jp</a>, Fujisawa Pharmaceutical</td>
<td>ARAI, Hiroyuki</td>
</tr>
<tr>
<td>English translation</td>
<td><a href="mailto:ishidat@je-medlang.com">ishidat@je-medlang.com</a>., Japan Med Linguistics Inst</td>
<td>ISHIDA, Takumi</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:ldhavens@gol.com">ldhavens@gol.com</a>, Free-lance</td>
<td>L. Douglas Havens</td>
</tr>
<tr>
<td>Liaison</td>
<td><a href="mailto:miyazawa@jpma.or.jp">miyazawa@jpma.or.jp</a></td>
<td>MIYAZAWA, Seiji</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:matsuki@jpma.or.jp">matsuki@jpma.or.jp</a>, JPMA</td>
<td>MATSUKI, Tatsuhiko</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:international@jpma.or.jp">international@jpma.or.jp</a>, JPMA</td>
<td>KAZAMA, Setsuko</td>
</tr>
<tr>
<td></td>
<td><a href="mailto:hirai-k@jpma.orjp">hirai-k@jpma.orjp</a>, JPMA</td>
<td>HIRAI, Kazuyoshi</td>
</tr>
</tbody>
</table>
APPENDIX

Japanese Pharmaceutical Regulations and Administration

March 2003

Edited by English Regulatory Information Task Force

©Japan Pharmaceutical Manufacturers Association
Torii-Nihonbashi Bldg., 3-4-1 Nihonbashi-Honcho, Chuo-ku, Tokyo 103-0023, Japan
Phone 81-3 (3241) 0326    Fax 81-3 (3242) 1767

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