

Pharmaceuticals and Medical Devices Safety Information

No. 229 October 2006

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* is issued based on safety information collected by the Ministry of Health, Labour and Welfare. It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. PMDSI is available on the Pharmaceuticals and Medical Devices Agency website (<http://www.pmda.go.jp/english/index.html>) and on the MHLW website (<http://www.mhlw.go.jp/>, Japanese only).

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*This translation of the original Japanese text is for information purpose only
(in the event of inconsistency, the Japanese text shall prevail).*

Pharmaceuticals and Medical Devices Safety Information

No. 229 October 2006

Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare, Japan

[Outline of Information]

No.	Subject	Measures	Outline of information	Page
1	Guidance for bar code labeling on prescription drugs for the prevention of medical accident		<p>The practice of bar code labeling on prescription drugs has been notified to promote prevention of accidents due to mix-ups and traceability of drugs. This section presents the background, summary, and implementation dates of the practice, etc.</p> <p>The objectives of the notified “New Bar code Labeling” are the followings: by labeling a product-specific, machine-readable bar code for each unit of prescription drugs (e.g., each ampule),</p> <ul style="list-style-type: none"> • to identify products mechanically for the prevention of medical accident due to mix-ups. • to record the trace of drugs from manufacturers and distributors to patients for the secure traceability. 	3
2	Project of Early Post-marketing Phase Safety Information collection (fixed-point observation project)		<p>For post-marketing safety measures for drugs, it is important how fast and accurate the information such as adverse reactions occurred in medical settings are collected. In the Pharmaceutical Affairs Law (PAL), the system of reporting adverse reactions from marketing authorisation holders and healthcare providers has been established. This section presents a project of Early Post-marketing Phase safety information collection, which has been conducted since 2006 with the objective of establishing a network for information collection.</p>	8
3	Automated external defibrillator (AED) without indication for children under age of 8		Revision of PRECAUTIONS (No. 180)	10
4	Products subject to Early Post-marketing Phase Vigilance		Lists products subject to Early Post-marketing Phase Vigilance as of October 1, 2006.	11

D: Distribution of Dear Healthcare Professional Letters *P*: Revision of PRECAUTIONS *C*: Case Reports

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, they are obligated to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorisation holder. As medical and pharmaceutical providers, drug retailers with a second-class license and household distributors are also required to report safety issues related to drugs and medical devices.

Guidance for bar code labeling on prescription drugs for the prevention of medical accident

1. Introduction

This section presents the background, summary, and implementation dates of the practice, etc. for the guidance for bar code labeling on prescription drugs to prevent medical accident because the “Practice of Bar Code Labeling on Prescription Drugs”, the PFSB/SD Notification No. 0915001 of Director of Safety Division of Pharmaceutical and Food Safety Bureau (PFSB), Ministry of Health, Labour and Welfare (MHLW), dated September 15, 2006, that has been issued to request marketing authorization holders for proper bar code labeling.

2. Background

MHLW has been discussed on measures for prevention of medical accident which may occur due to the similarity of drug names and appearances. In May 2000, the “Discussion Group on Measures for Prevention of Drug and Medical Device-related Medical Accident” was established. After May 2001, the detailed measures have been discussed in the “Discussion Group on Medical Safety Measures, Division of Drugs and Medical Devices” and in its branch of the “Working Group on Drug Similarity”.

Based on the discussions in these groups, the following notifications have been issued:

- ① PMSB Notification No. 935 of Secretary-General of PMSB, MHLW, dated September 19, 2000
“Handling of Labels and Brand Names of Drugs for the Prevention of Medical Accident”, etc.
- ② PFSB Notification No. 1127003 of Secretary-General of PFSB, MHLW, dated November 27, 2003
“Thoroughness of Measures for the Prevention of Medical Accident Due to the Similarity of Drug Brand Names and Appearances”, etc.
- ③ PFSB Notification No. 0602009 of Secretary-General of PFSB, MHLW, dated June 2, 2004.
“Reinforcement and Thoroughness of Measures for the Prevention of Drug-related Medical Accident”, etc.

These notifications intend to guide relevant companies to active participation in measures, including the improvement of precaution labels for drugs with dosage forms that are easy to misuse, the standardization of labeling items on packages such as PTP sheets (brand name, specification, and dosage, etc.), the establishment of naming rules for the brand names of drugs. These information have been introduced in the “Pharmaceuticals and Medical Devices Safety Information” No. 163 (November 2000) and No. 202 (June 2004).

In addition to the measures mentioned above such as the improvement of labeling, the fundamental measures, such as dispensing check by methods other than visual check, have been suggested to be necessary to prevent mix-ups of drugs. First, the standardization of code labels for drugs was proposed in the “Promotion of Total Medical Safety Measures” prepared on April 2002 by the “Discussion Group on Medical Safety Measures” comprising of experts. The objective was to further promote the use of bar code check to be implemented by the government to perform accurate and easy product distinction by the use of bar code check. Then, on December 2003, as the measures on “products” such as drugs, the “Urgent Appeal for Measures of Medical Accident” of the Minister of Health, Labour and Welfare was issued to

require thoroughness of the safety control of drugs by, for example, using two-dimensional codes and IC tags. In light of these developments, MHLW has determined to promote dispensing information check not only by visually but also by mechanically, i.e., the standardization of bar code labels on drugs, to prevent medical accident due to mix-ups. Therefore, on May 2004, the Discussion Group on Standardization of Code Labeling was established and has discussed on coding system and other issues. Based on the coding system for product identification (the JAN based coding system), which was reported by the Discussion Group on September 2005, the “Practice of Bar Code Labeling on Prescription Drugs (draft)” was prepared.

In response, the public comments on the “Practice of Bar Code Labeling on Prescription Drugs (draft)” were collected from March 24 to June 15, 2006. Based on the collected comments and the previous discussions, the “Practice of Bar Code Labeling on Prescription Drugs”, the PFSB/SD Notification No. 0915001 of Director of Safety Division of PFSB, MHLW, dated September 15, 2006 was presented.

3. Summary of Bar Code Labeling on Prescription Drugs

(1) Objectives

By labeling a product-specific, machine-readable bar code for each unit of prescription drugs (e.g., each ampule),

- to identify products mechanically for the prevention of medical accident due to mix-ups.
- to record the trace of drugs from marketing authorization holders and distributors to patients for the secure traceability.

(2) Products subject to labeling and labeling data

The products subject to labeling are prescription drugs, which are classified to the following five categories:

- ① Specific biological product
- ② Biological product (excluding specific biological product)
- ③ Oral medicine [excluding ① and ②]
- ④ Injection drug [excluding ① and ②]
- ⑤ External medicine [excluding ① and ②]

Package types are categorized into the following three units. According to the type of prescription drugs, a product code, expiration date, a lot number or manufacturing code, and a quantity are displayed.

- Dispensing packaging unit
A dispensing packaging unit is the minimum packaging unit in which marketing authorization holders pack drugs for marketing.
For example, it would be a PTP sheet or a bottle for tablets and capsules, or an ampule or a vial for injection drug.
- Distribution packaging unit
A distribution packaging unit is usually the minimum packaging unit in which sellers such as wholesalers sell products to buyers such as medical institutions.
For example, it would be a box of 100 dispensing packaging units, i.e., PTP sheets, for tablets and capsules, or a box of 10 ampules for injection drug.
- Supply packaging unit
A supply packaging unit is usually a packaging unit comprising a multiple distribution packaging unit packed by marketing authorization holders.
For example, it would be a carton box containing 10 distribution packaging units of boxes.

*"The marks ⊙ indicate that labeling is necessary (required labeling)" and "○ indicate that labeling is not necessary (optional labeling)".

Types of prescription drugs	Dispensing packaging unit			Distribution packaging unit			Supply packaging unit			
	Product Code	Expiration Date	Lot Number	Product Code	Expiration Date	Lot Number	Product Code	Expiration Date	Lot Number	Quantity
① Specified biological product	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊙
② Biological product ^(note 1)	⊙	○	○	⊙	⊙	⊙	⊙	⊙	⊙	⊙
③ Oral medicine ^(note 2)	⊙	○	○	⊙	○	○	○	○	○	○
④ Injectable drug ^(note 2)	⊙	○	○	⊙	○	○	○	○	○	○
⑤ External medicine ^(note 2)	⊙	○	○	⊙	○	○	○	○	○	○

(note 1) Excluding specified biological product.

(note 2) Excluding biological product (and specified biological product as well).

(3) Numbering product codes and JAN codes

- 1) A product code is a 14-digit code starting with "0" for dispensing packaging unit, "1" for distribution packaging unit, and "2" for supply packaging unit, which is displayed at the front of JAN code for each packaging unit for each drug.
- 2) Numbering rule for a JAN code
 - A JAN code should be assigned for each type of packaging unit for each drug. For example, in medical settings, it is necessary to avoid mix-ups between PTP sheets containing 10 tablets and 21 tablets. Thus, for dispensing packaging, PTP sheets of 10 tablets and 21 tablets should be handled as different types.
 - For supply packaging, a JAN code should be the same for a corresponding distribution packaging. Therefore, JAN codes for dispensing packaging and distribution packaging should be different.
 - Different JAN codes should be numbered for each distribution company.
 - A previously used JAN code should not be reused for at least 10 years after the drug with the JAN code was out of the market. However, JAN codes used for specified biological products should never be reused.

(4) Rules for JAN code changes associated with changes such as in names and ingredients.





(5) Bar code symbol system, display order of data elements, and application identifiers

- 1) Dispensing packaging and distribution packaging

When displaying a lot number or manufacturing code and an expiration date in addition to a product code, RSS Limited Composite Symbol with CC-A (RSS Limited) is used. RSS-14 Stack Composite Symbol with CC-A (RSS-14 Stack) may be used when a display area is small.

RSS Limited is used when displaying only a product code. RSS-14 Stack may be used when a display area is small.

Example of RSS code labeling

Detail of symbol	Positive symbol (Print, thermal transfer printer)	Negative symbol (Laser marker)
RSS-14 Stack	 (01)04987999000005	 (01)04987999000005
RSS Limited	 (01)04987999000005	 (01)04987999000005

2) Supply packaging

Code 128 is used.

Example of code 128 labeling



(01)2498711111118(17)060915(30)10000(10)123456

(01) Product code	(17) Expiration date	(30) Quantity	(10) Lot number
----------------------	-------------------------	------------------	--------------------

Display order: 1

2

3

4

} Data elements
and application
identifiers

(6) Implementation date of new bar-code labeling

- 1) All kinds of packaging units for specified biological product, biological product or injectable drug (excluding biological product) or distribution packaging unit for oral medicine (excluding biological product) or external medicine (excluding biological product): All products released by manufacturers on September 2008 and later should have new bar code labels (for the products in special circumstances, e.g., products only manufactured once a year, implementation data will be September 2009).
- 2) Dispensing packaging unit for oral medicine (excluding biological product) or external medicine (excluding biological product): The implementation date will be notified separately since technologies, such as bar code labeling for each packaging style, are under development and aimed to be implemented in 3 to 5 years by relevant industries and companies.

(7) Others

- 1) The bar codes of Japanese Industrial Standards (JIS) X0501 (bar code symbol for uniform commodity code) that are currently displayed on distribution packaging units and JIS X0502 (bar code symbol for dispatch unit code) displayed on supply packaging units should be displayed with new bar code labels for at least 5 years after guidance for new bar code labeling on distribution packaging units and supply packaging units of prescription drugs.
- 2) Among the information encoded in a bar code label, the management of product code, which specifies drugs, should be unified for smooth utilization in medical institutions. Therefore, distributors of each product are required to register product codes to the Medical Information System Development Center (MEDIS-DC), which will manage the product codes and provide the data to medical institutions.
- 3) Regarding the data for which labeling is not necessary (optional labeling), future expansion of products subject to labeling will be discussed based on the future status of labels and its use.

4. Closing comments

The practice of bar code labeling, including the codes to be used, data elements to be displayed, and implementation date, have been summarized in the “Practice of Bar code Labeling on Prescription drugs”. Upon guidance for bar code labeling according to this practice, the use of bar code labels for information such as product codes for prescription drugs is expected to result in benefits such as the prevention for medical accident due to mix-ups and the establishment of an environment that allows more accurate checking on the lot numbers or expiration dates of biological products. Furthermore, the expected benefits in medical institutions would be the improved efficiency in checking incoming products and taking inventory in pharmacy departments, the security of proper inventory in in-house distribution, as well as the more efficient and accurate dispensing check by verifying the drugs with the dispensing information.

It is requested that medical institutions generously understand and cooperate on bar code checking to help the bar code system to be widely adapted and used.

<Related URL>

- The discussion results in the “Working Group on Drug Similarity” (MHLW website)
<http://www.mhlw.go.jp/shingi/2004/03/s0302-8.html> (In Japanese)
- “Practice of Bar code Labeling on Prescription drugs” (PFSB/SD Notification No. 0915001 dated on September 15, 2006)
(Pharmaceuticals and Medical Devices Information Website)
http://www.info.pmda.go.jp/iryoushiki/iryoushiki_index.html (in Japanese)
- The public comments on the “Practice of Bar code Labeling on Prescription Drugs”
http://search.e-gov.go.jp/servlet/Public?ANKEN_TYPE=3&OBJCD=100495 (in Japanese)

Project of Early Post-marketing Phase Safety Information collection (fixed-point observation project)

1. Introduction

For post-marketing safety measures for drugs, it is important how fast and accurate the information such as adverse reactions occurred in medical settings are collected. In the Pharmaceutical Affairs Law (PAL), the system of reporting adverse reactions from marketing authorisation holders and healthcare providers has been established (Article 77-4-2 of the PAL).

In addition, with the objective of establishing some networks for information collection, the project of Early Post-marketing Phase safety information collection has been conducted since FY 2006.

For the newly approved drugs that are more novel or less used in Japan and overseas, the safety especially in Early Post-marketing Phase should be ensured. Therefore, this project is conducted by the government, which directly collects and evaluates information in clinical practice, such as statuses of use and incidence of adverse drug reaction, for 6 months after drugs are marketed in principle to enhance and improve safety measures.

2. Selection of Drugs Subject to the Project

Drugs subject to the project (hereafter referred to as “Target Drugs”) are, in principle, newly approved drugs with any of the following characteristics, for which the safety especially in Early Post-marketing Phase should be ensured.

- ① Drugs that are considered to be more novel ^{note 1)}
- ② Drugs for which drug use-result survey in all patients are required as an approval condition (excluding orphan drugs)
- ③ Drugs that are less used in Japan and overseas ^{note 2)}

Note 1) Drugs are considered to be more novel when there are no other drugs with similar chemical structures and pharmacological effects that have been approved in Japan.

Note 2) For example, drugs for which clinical trials in Japan were conducted in a few subjects (about less than 50 subjects) or those that have not been marketed in major Western countries.

Target Drugs will be determined based on the opinions from members of Committee on Safety of Drugs, Pharmaceutical Affairs and Food Sanitation Council. The selection results will not be announced until the project is completed since it is conducted independently from Early Post-marketing Phase Vigilance by marketing authorisation holders of Target Drugs.

3. Selection of Investigators, etc.

The project will be cooperated by physicians and pharmacists from approximately 6 medical institutions in Japan (including pharmacies etc. that accept prescriptions from the same medical institutions).

Physicians and pharmacists with extensive knowledge and experience in the specialized area will be

selected, based on the opinions from members of Committee on Safety of Drugs, Pharmaceutical Affairs and Food Sanitation Council, from medical institutions which participate in the clinical trials or expect to use the Target Drugs in numbers of patients. Consideration in the selection should include regional balance, size of affiliated medical institution, and establishment entity.

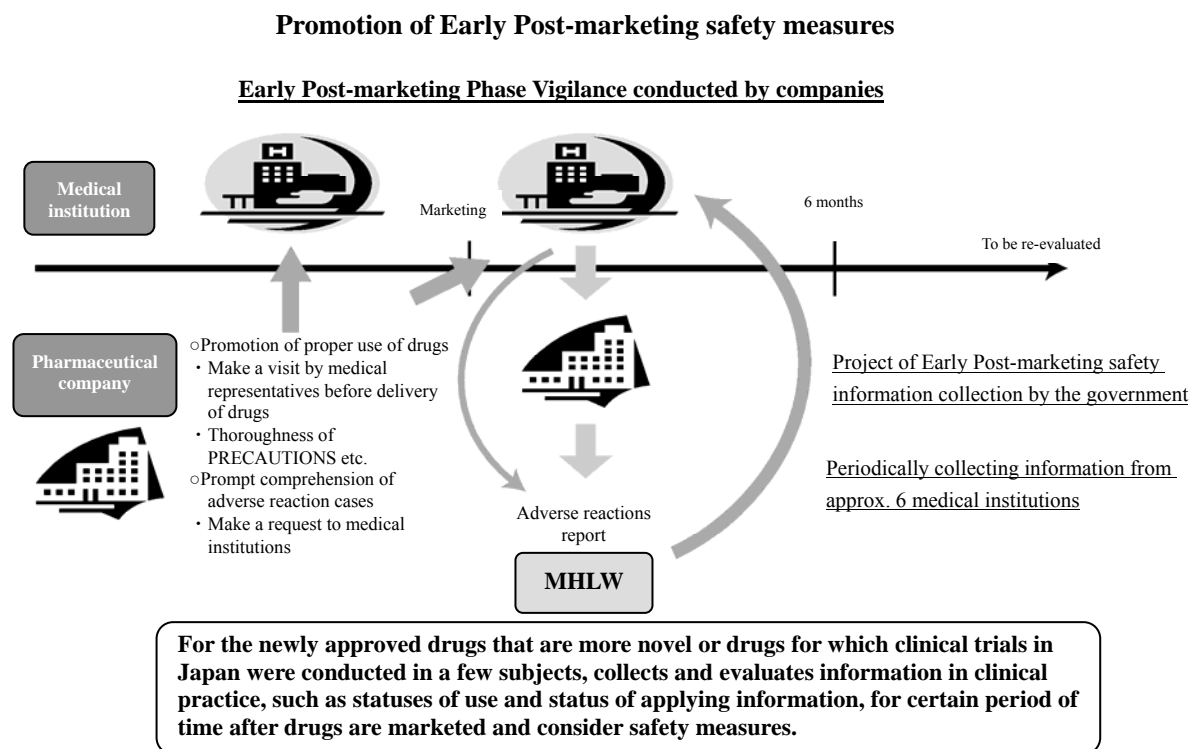
The selection results are not to be announced until the project is completed as in the selection of Target Drugs.

4. Project Flow

This project is conducted, in principal, for 6 months after Target Drugs are marketed. Physicians and pharmacists from each medical institution are asked to report the following information periodically. Necessary safety measures are then ensured.

- Statuses of use and incidence, including adverse reaction, for Target Drugs
- Status of providing information on Target Drugs by marketing authorisation holders
- Status of applying safety control information in each medical institution
- Other Target Drug-related information

After completion of the project, the summary is to be reported to the current Committee on Safety of Drugs, Pharmaceutical Affairs and Food Sanitation Council.



5. Closing comments

Safety measures for drugs are aimed to be enhanced and improved in the future by conducting this project in addition to conventional safety measures provided through pharmaceutical companies.

Your positive cooperation will be greatly appreciated when selected as an attending for this project.

Revision of PRECAUTIONS

(No. 180)

Medical Devices

This section presents details of the revisions to the PRECAUTIONS section of the package inserts of medical devices in accordance with the Notification after the previous issue (Pharmaceuticals and Medical Devices Safety Information No. 228).

1 Automated External Defibrillators (AEDs) Without Indication regarding Defibrillation for Small Children Younger than 8 Years of Age*

* Excluding AEDs with non-approved indication regarding pediatric use

[Use in Children]

Adult AED pads should be used to small children between 1 and younger than 8 years of age only if it is absolutely necessary, such as no AED with pediatric AED pads are available on the scene, because its efficacy and safety have not been identified.

- When adult AED pads are used to such children, extra caution should be required to avoid electric contact between two pads.
- Do not use in infants younger than 1 year of age.

<Reference Information>

- 1) HPB/GMSD Notification No. 0825001 issued by the Director of Guidance of Medical Service Division, the Health Policy Bureau, Ministry of Health, Labour and Welfare, dated on August 25, 2006
“Summary of Emergency Resuscitation Guidelines (for General Public) including how to use AEDs”
- 2) FDMA/ARSD Notification No. 110 issued by the Director of Ambulance Service Planning Office, the Fire and Disaster Management Agency, dated on August 15, 2006
“Report of “Discussion Group for Promotion of Advanced Emergency Service””
- 3) Japan Foundation for Emergency Medicine [New Guidelines for Emergency Resuscitation in Japan (Outline)]
<http://www.qqzaidan.jp/qqsosei/index.htm>

4

List of products subject to Early Post-marketing Phase Vigilance

(As of October 1, 2006)

Nonproprietary name ----- Brand name	Name of the marketing authorisation holder	Date of EPPV initiation
Interferon Beta ----- Feron* ¹	Toray Industries, Inc.	April 20, 2006
Epoetin Beta (Genetical recombination) ----- Epogin Injection Ampoule 750, 1500, and 3000, Epogin Injection Syringe 750, 1500, and 3000* ²	Chugai Pharmaceutical Co., Ltd.	April 20, 2006
Somatropin (Genetical recombination) ----- Humatrope C 6 mg and 12 mg* ³	Eli Lilly Japan K.K.	April 20, 2006
Zoledronic Acid Hydrate ----- Zometa Injection 4 mg* ⁴	Novartis Pharma K.K.	April 20, 2006
Micafungin Sodium ----- Funguard 50 mg and 75 mg for Infusion* ⁵	Astellas Pharma Inc.	April 20, 2006
Linezolid ----- Zyvox Tablets 600 mg, Zyvox Injection 600 mg* ⁶	Pfizer Japan Inc.	April 20, 2006
Tosufloxacin Tosilate ----- Tosuflo Ophthalmic Solution 0.3%	Nidek Co., Ltd.	April 28, 2006
Clopidogrel Sulfate ----- Plavix Tablets 25 mg and 75 mg	Sanofi-Aventis K.K.	May 8, 2006
Silodosin ----- Urief Cap. 2 mg and 4 mg	Kissei Pharmaceutical Co., Ltd.	May 11, 2006
Tosufloxacin Tosilate ----- Ozex Ophthalmic Solution 0.3%	Toyama Chemical Co., Ltd.	May 11, 2006
Follitropin Alfa (Genetical recombination) ----- Gonalef for SC Injection 75 and 150	Serono Japan Co., Ltd.	May 11, 2006
Letrozole ----- Femara Tablets 2.5 mg	Novartis Pharma K.K.	May 11, 2006
Loxoprofen Sodium ----- Loxonin PAP 100 mg	Lead Chemical Co., Ltd.	May 23, 2006
Aripiprazole ----- Abilify Tablets 3 mg and 6 mg, Abilify Powder 1%	Otsuka Pharmaceutical Co., Ltd.	June 8, 2006
Solifenacin Succinate ----- Vesicare Tablets 2.5 mg and 5 mg	Astellas Pharma Inc.	June 8, 2006
Tolterodine Tartrate ----- Detrusitol Capsules 2 mg and 4 mg	Pfizer Japan Inc.	June 8, 2006
Amphotericin B ----- AmBisome for Intravenous Infusion 50 mg	Dainippon Sumitomo Pharma Co., Ltd.	June 20, 2006
Magnesium Sulfate/Glucose ----- Magsent Injection 100 mL	TOA Pharmaceuticals Co., Ltd.	June 20, 2006

Sertraline Hydrochloride ----- Jzoloft Tablets 25 mg and 50 mg	Pfizer Japan Inc.	July 7, 2006
Somatropin (Genetical recombination) ----- Genotropin 5.3 mg, Genotropin Inj. 12 mg, Genotropin MiniQuick s.c. Inj. 0.6 mg, 1.0 mg, and 1.4 mg ^{*7}	Pfizer Japan Inc.	July 26, 2006
Inulin ----- Inulead Inj.	FUJIYAKUHIN Co., Ltd.	August 22, 2006
Alendronate Sodium Hydrate ----- Fosamac Tablets 35 mg	Banyu Pharmaceutical Co., Ltd.	September 15, 2006
Alendronate Sodium Hydrate ----- Bonalon Tablet 35 mg	Teijin Pharma Limited	September 15, 2006
Itraconazole ----- Itrizole Oral Solution 1%	Janssen Pharmaceutical K.K.	September 15, 2006
Temozolomide ----- Temodal Capsules 20 mg and 100 mg	Schering-Plough K.K.	September 15, 2006
Budesonide ----- Pulmicort Respules 0.25 mg and 0.5 mg	AstraZeneca K.K.	September 15, 2006
Entecavir Hydrate ----- Baraclude Tablets 0.5 mg	Bristol Pharmaceuticals Y.K.	September 21, 2006
Cetorelix Acetate ----- Cetrotide for Injection 0.25 mg and 3 mg	Nippon Kayaku Co., Ltd.	September 21, 2006
Manganese Chloride Tetrahydrate ----- Bothdel Oral Solution 10	Meiji Dairies Corporation	September 25, 2006
Gabapentin ----- Gabapen Tablets 200 mg, 300 mg, and 400 mg	Pfizer Japan Inc.	September 25, 2006

Note) Subject to additional indication etc.

*1: An additional indication for “the improvement of viremia in compensated cirrhosis type C (except in the patients with HCV serogroup 1 and high blood HCV-RNA level)”

*2: An additional indication for “anemia of prematurity”

*3: An additional indication for “adult growth hormone hyposecretion (severe cases only)”

*4: An additional indication for “bone lesions due to multiple myeloma and solid tumor metastases to bone”

*5: An additional administration for “pediatrics”

*6: An additional indications for “<Susceptible strains> methicillin-resistant Staphylococcus aureus (MRSA) sensitive to this drug <Indications> sepsis, deep skin infection, chronic pyoderma, secondary infection such as from traumatic injury/fever and surgical wound, and pneumonia”

*7: An additional indication for “adult growth hormone hyposecretion (severe cases only)”

Reference Material

Research on the occurrence status of influenza-associated symptoms

The study report of the “Research on the Occurrence Status of Influenza-associated Symptoms”, which was conducted as a Health and Labour Scientific Research in FY 2005, is presented.

This study report, including Appendices 1 to 4, is available on MHLW website (<http://www.mhlw.go.jp/>) (in Japanese).

Ministry of Health, Labour and Welfare Grant
Fiscal Year 2005 Final Study Report

“The research on the manifestation of influenza-associated symptoms”

(Principal Investigator) Shunpei Yokota
(Professor of the Department of Child Health and Development, Yokohama City University
School of Medicine)

Summary of research

Influenza is a disease associated with various symptoms. Encephalopathy in infants has been a major issue in Japan. Characteristic abnormal behaviours have been observed in infants with influenza encephalopathy during development of convulsion and disturbed consciousness after pyrexia onset. However, it is unknown whether those are prodromes of influenza encephalopathy, general symptoms associated with influenza, or the effects of drugs used for the treatment. Therefore, we asked pediatricians in 12 prefectures including Tokyo to complete the “Questionnaire for Physicians” and to have their patients’ families to complete the “Questionnaire for Patients/Patients’ Families” with information such as clinical symptoms occurred during the course of influenza, drugs used, and individual progresses of influenza, and statistically analyzed the data following collection of completed forms. Associated symptoms occurred mostly on Day 1 and Day 2 of pyrexia onset, which accounted for 92% of total number of incidence. The drug use was also frequent on Day 1 and Day 2, i.e., 95.4% for Acetaminophen and 91.8% for Tamiflu. Assessment of relationship between drug use and clinical symptoms revealed that there was no significant difference in incidence of abnormal behaviours between non-Tamiflu users and Tamiflu users, i.e., 10.6% vs 11.9%. When abnormal behaviours and Tamiflu use occurred in the same period, hazard ratios for the incidence under the assumption that Tamiflu was used before and after the symptom onset were 1.16 and 0.90, respectively. The corresponding *P* values were 0.259 and 0.463, indicating no significant difference in the incidence between Tamiflu users and non-Tamiflu users. For pneumonia complication, the cumulative incidences were 3.1% in non-Tamiflu users and 0.7% in Tamiflu users. The hazard ratios under the assumption that Tamiflu was used before and after the complication onset, were 0.24 (*P* <0.0001) and 0.20 (*P* <0.0001), respectively. Thus Tamiflu suppressed pneumonia in both cases. More precise investigation on the time relationship between associated symptoms and drug use would be needed in next season.

Associated researchers: Mori Masaaki (Department of Child Health and Development, Yokohama City University School of Medicine), Morishima Tsuneo (Department of Pediatrics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences), Atsuo Nezu (Department of Pediatrics, Yokohama City University General Medical Center), Okumura Akihisa [Department of Pediatrics, Nagoya University (currently at the Department of Pediatrics, Juntendo University)], Hosoya Mitsuaki (Department of Pediatrics, Fukushima Prefectural University), Hiroshi Suzuki (Department of International Infectious Disease, Niigata University), Fujita Toshiharu (The Institute of Statistical Mathematics)

A. Background and Objectives

Influenza is a disease associated with various symptoms. In particular, influenza encephalopathy in infants has been a major issue in Japan. Previous investigations by the study group of MHLW and by the family association revealed that characteristic abnormal behaviours occur in infants with influenza encephalopathy during development of convulsion and disturbed consciousness after pyrexia onset. However, it is unknown whether these abnormal behaviours may be considered as prodromes of influenza encephalopathy or as general symptoms associated with influenza. Therefore, an investigation of the association with influenza itself has become essential. In addition, the development of avian influenza mutations has become a concern for human infection, leading to a need for epidemiological investigations on general and associated symptoms of currently prevalent influenza. On the other hand, the development of rapid diagnostic procedures has allowed to prescribe anti-influenza drugs to patients with diagnosed influenza, which has been an almost standard medical practice for influenza. However, actual prescription status and its association with progress of general and associated symptoms of influenza have not been fully investigated.

Taking all the issues into account, this study was conducted to investigate influenza-associated symptoms and actual prescription status for the disease.

B. Methods

1. Investigation Procedures

- “Questionnaire for Physicians” (Appendix 1) and “Questionnaire for Patients/Patients’ Families” (Appendix 2) were distributed to pediatricians from 12 prefectures including Tolyo. The physicians and their patients’ families were asked to complete the forms with information such as clinical symptoms occurred during the course of influenza, drugs used, and individual progresses of influenza. The completed forms were collected and the data were statistically analyzed.
- First, physicians decided the date of study initiation. Starting on the date, 10 consecutive patients with influenza, which was diagnosed by methods such as rapid diagnostic procedures,

were asked to complete <Questionnaire for Patients/Patients’ Families>.

- At the same time, physicians completed <Questionnaire for Physicians> for the selected patients. Physicians collected the patients’ completed questionnaires on their revisit after Day 7 of disease. Information of patients who could not revisit was collected by other means such as phone.
 - A completed <Questionnaire for Patients/Patients’ Families> was submitted on patient’s revisit and matched with a completed <Questionnaire for Physicians> with the same serial number. All forms for 10 patients were sent together to the research team.
 - This study was conducted after approval of Yokohama City University Ethical Committee, where the principal investigator belonged.
- ### 2. Questionnaire for Physicians (Appendix 1)
- The first day of pyrexia onset was designated as “Day 1 of disease”. The highest body temperature was recorded from Day 1 to Day 7 of disease.
 - A day was divided into <Morning>, <Afternoon>, and <Night>. <Morning>, <Afternoon>, and <Night> were defined as 6 am to noon, noon to 6 pm, and 6 pm to 6 am next day, respectively.
 - “Clinical Symptoms” were specified by physicians’ observations. For abnormal behaviours, examples were described on the back of questionnaire form for reference. Boxes for abnormal behaviours were marked when patients showed relevant behaviours.
 - Prescriptions of “Remedies” were recorded starting at the initial dose.
 - For symptoms, boxes were marked with “✓” when observed and “?” when not clear, or left “blank” when not observed.
 - When a patient was transferred to another hospital due to worsening condition, the transferred hospital was specified.
- ### 3. Questionnaire for Patients/Patients’ Families (Appendix 2)
- The consent and explanation documents (Appendix 3) was provided to patients’ families prior to the study to request for their participation.

- For “pyrexia”, the first day of pyrexia onset was designated as “Day 1 of disease”. The highest body temperature of the day was recorded from Day 1 to Day 7 of disease.
 - For “Symptoms”, examples were described on the back of questionnaire form for reference.
 - ① For the observation of each symptom from Day 1 to Day 7 of disease, one of the numbers “1. Observed, 2. Not observed, 3. Unclear” was circled. It was noted that infants may not be able to complain symptoms such as myalgia, arthralgia, ear pain, pain pharynx, and headache. The number “3” (Unclear) was circled only when existence or nonexistence of symptoms could not be judged.
 - ② Boxes for the days of symptom onset (Morning/Afternoon/Night) were marked with “✓” when symptoms were observed, i.e., “1.” (Observed) was circled, and with “?” when existence or nonexistence of symptoms were unclear, or left blank when symptoms were not observed.
 - ③ The definitions of <Morning>, <Afternoon>, and <Night>, which were 6 am to noon, noon to 6 pm, and 6 pm to 6 am next day, respectively, were also noted.
 - For “Remedies”, patient’s families used the content of prescriptions received from their physicians as reference.
 - ① Appropriate number was circled to indicate the use of each drug.
 - ② Boxes for the times of drug use, i.e., Morning/Afternoon/Night, were marked with “✓” when drugs were used and left blank when drugs were not used.
 - Patients’ families were instructed to ask their physicians when they have any questions regarding the questionnaire.
- C. Results (Appendix 4)
- The number of completed questionnaires collected was 2846 from physicians and 2545 from patients/patients’ families (Appendix Appendices 4-1).
 - The pediatric subjects were almost evenly spread across the pediatric age range. Only 35.9% of the patients have had two vaccinations. Convulsion was previously occurred in 4.3% of patients (Appendix 4-2).
 - Pyrexia of 38°C or higher was developed on Day 1 and Day 2 of disease. Abnormal behaviours were observed in 10.5% of patients, which was a higher than previously reported. Further investigations are needed for verification. Other observed clinical symptoms included convulsion (0.6%), febrile convulsion (2.6%), disturbed consciousness (1.3%), pneumonia (1.4%), croup (1.7%), otitis media (1.3%), myositis (1.0%). These incidences were comparable to those of influenza-associated symptoms reported previously [Appendix 4-3 ①]. For drugs, the majority (90.0%) of patients used Tamiflu. Few patients used acetaminophen (39.6%) and antibacterial drugs (28.0% in total) [Appendix 4-3 ②]. This indicates that antibacterial drugs were not prescribed due to diagnosis from rapid diagnostic procedures.
 - Each clinical symptom occurred mostly on Day 1 or Day 2 of disease, which accounted for around 90% of total number of incidence. In particular, the incidence of abnormal behaviours on the both days was 95.6%. However, it was not true for otitis media, which continued to occur with a rate of a few percent until Day 7 of disease (Appendix 4-4).
 - For times of drug use, 95.4% and 91.8% of the use of acetaminophen and Tamiflu occurred on Day 1 or Day 2 of disease, respectively. Antibacterial drugs were administered even after Day 3 of disease (Appendix 4-5).
 - For duration of clinical symptoms, abnormal behaviours, convulsion, febrile convulsion, and disturbed consciousness persisted for a relatively short period of time, i.e., 1 day or 2 days (Appendix 4-6).
 - Assessment of relationship between drug use and clinical symptoms revealed that there is no significant difference in incidence of abnormal behaviours between Tamiflu users and non-Tamiflu users, i.e., 10.6% vs 11.9%. When abnormal behaviours and Tamiflu use occurred in the same period, hazard ratios for the incidence under the assumption that Tamiflu was used before and after the symptom onset were 1.16 and 0.90, respectively. The corresponding *P* values were 0.259 and 0.463, indicating no significant difference in the incidence between Tamiflu users and non-Tamiflu users [Appendix 4-7 ①]. In the present study, time relationship between Tamiflu use and abnormal behaviours could not be

assessed since no instruction was given to specify when the events occurred. This subject matter should be investigated in the next study.

- For pneumonia complication, the cumulative incidences were 3.1% in non-Tamiflu users and 0.7% in Tamiflu users. The hazard ratios under the assumption that Tamiflu was used before and after the complication onset, were 0.24 ($P < 0.0001$) and 0.20 ($P < 0.0001$), respectively. Thus, Tamiflu suppressed pneumonia in both cases (Appendix 4-7 ⑤). Tamiflu also suppressed croup complication (Appendix 4-7 ⑥).
- No correlation was observed between Tamiflu use and development of convulsion, febrile convulsion, or disturbed consciousness and concurrent otitis media/myositis (Appendices 4-7 ② to ④, ⑦ and ⑧).
- Patients who used acetaminophen had significantly higher incidence of clinical symptoms, including abnormal behaviours, convulsion, febrile convulsion, and disturbed consciousness (Appendices 4-8 ① to ④).
- No correlation was observed between acetaminophen use and development of concurrent pneumonia, croup, otitis media, and myositis (Appendices 4-8 ⑤ to ⑧).
- Relationship between drug use and increased incidence was observed for macrolide antibiotics and concurrent pneumonia (Appendix 4-9), penicillin antibiotics and concurrent otitis media (Appendix 4-10), as well as cephem antibiotics and abnormal behaviour inhibition and concurrent pneumonia/croup (Appendices 4-11 ① to ③).
- The answers in “Questionnaire for Patients/Patients’ Families” also revealed that pyrexia of 38°C or higher was developed only on Day 1 and Day 2 on average. Abnormal behaviour was observed as frightening/fear in 8.7% of patients, visual hallucination/hallucination in 5.9%, sudden loudness/delirious words in 12.8%, anger/grin in 8.5%, and biting fingers in 0.7%. Other observed clinical symptoms included convulsion (3.1%), loss of consciousness (1.5%), sever cough (41.1%), vomiting/diarrhoea (35.0%), pain pharynx (40.4%), and headache (40.9%) (Appendix 4-12)
- Many cases of abnormal behaviour, convulsion, and loss of consciousness were developed at night on Day 1 of disease (Appendix 4-13 ①) Ear pain persisted until Day 5 of disease (Appendix 4-13 ②).
- The most commonly administered drug was Tamiflu, which was used by 92.1% of patients on Day 1 or Day 2 of disease (Appendix 4-14).
- For symptoms such as frightening/fear, visual hallucination /hallucination, and sudden anger, no significant difference was observed in the cumulative incidences between non-Tamiflu group and Tamiflu group (Appendices 4-15 ①, ②, and ④). When sudden loudness/delirious words and Tamiflu use occurred in the same period, the relationship between both events was different depending on the assumptions made for time of drug use (Appendix 4-15 ③).
- Tamiflu significantly suppressed sever cough (hazard ratio 0.69; $P < 0.0001$) (Appendix 4-15 ⑤).
- Multivariate study was performed because the incidence of clinical symptoms could be related to factors other than drugs. The results revealed that factors affecting the incidence of abnormal behaviour were age and the highest body temperature ($\geq 40.0^{\circ}\text{C}$) during the course (Appendix 4-16).
- No significant correlation was found between Tamiflu and abnormal behaviour after multivariate adjustment for sex, age, vaccination, asthma bronchial, convulsion, and pyrexia (hazard ratio 1.07; $P = .647$) (Appendix 4-17 ①).
- After the above multivariate adjustment, there was also no significant relationship between Tamiflu and incidences of convulsion, febrile convulsion, and disturbed consciousness (Appendices 4-17 ② to ④).
- After multivariate adjustment for the effects of the related factors, the relationship between acetaminophen and febrile convulsion disappeared (Appendix 4-17 ③). However, a trend toward an increase in incidence of abnormal behaviour and convulsion still remained (10% level of significance) (Appendices 4-17 ① and ②), and incidence of disturbed consciousness significantly increased (Appendix 4-17 ④). In the future, more precise investigations should be conducted to verify

these results.

- After the above multivariate adjustment, the significant relationship was found between Tamiflu and suppressed concurrent pneumonia as well as cephem antibiotics and increased concurrent pneumonia (Appendix 4-17 ⑤).

D. Conclusions

- The present study analyzed the data of about 2500 patients collected from both physicians and their patients/patients' family.
- Collection of more precise information was made possible by distributing questionnaires to individual physicians and their patients' families.
- The incidence of abnormal behaviours was 10%, which was very high compared to the previous reports. The symptoms may be excessively reported because the definition and description of abnormal behaviours are somewhat vague and influenza-associated abnormal behaviours have been repeatedly reported mainly by media since the end of last year. Conclusions should be made based on the results of follow-up studies in future years.
- This survey investigated the status of drug use and clinical symptoms on each day, which was divided into "Morning/Afternoon/Night", during the 7 days after pyrexia onset. When initial drug use and new onset of clinical symptoms occurred in the same period, the time relationship between the both events could not be specified.
- Each clinical symptom, including abnormal behaviour, occurred mostly on Day 1 or Day 2 of disease, which accounted for around 90% of total number of incidence. Thus, further

detailed investigations during these periods should be important.

- Multivariate study revealed no significant relationships between Tamiflu and abnormal behaviours, convulsion, febrile convulsion, and disturbed consciousness. However, further studies are needed to lead to definite conclusions.
- This study was meaningful etiologically and socially. Further larger-scale consideration for precise time-course assessment of events should be essential.
- It was reaffirmed that influenza is never a slight illness since it could be associated with various symptoms compared to common cold syndromes.

E. Issues in Studies in Future Years

- Since influenza-associated symptoms developed mostly on Day 1 and Day 2 of disease, the next study should be limited during these periods. Appropriate instructions should be given to physicians and patients' families to specify detailed description of abnormal behaviours in the comment section. The questionnaires should be modified so that time-course of symptoms (especially relationship with time of drug use) could be specified.
- Larger-scale surveys would be planned by expanding survey location.
- Real-time information should be processed to collect higher-quality data.
- More precise investigation on the time relationship between associated symptoms and drug use would be needed in the next season.