

# Pharmaceuticals and Medical Devices Safety Information

No. 346 September 2017

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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 (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) Medical Product Information web page (<http://www.pmda.go.jp/english/index.html>) and on the MHLW website (<http://www.mhlw.go.jp/>, only available in Japanese language).

Available information is listed here



Access to the latest safety information is available via PMDA Medi-navi.

Medi-navi is an email service that provides essential safety information released by the MHLW and PMDA. By registering, you can receive this information on the day of release.



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*This English version of PMDSI is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.*

# Pharmaceuticals and Medical Devices Safety Information

No. 346 September 2017

Ministry of Health, Labour and Welfare & Pharmaceutical Safety and Environmental Health Bureau, Japan

## [ Outline of Information ]

| No. | Subject                                                          | Measures | Outline of Information                                                                                                                                                                                                                                                                                                                       | Page |
|-----|------------------------------------------------------------------|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| 1   | The Expert Committee on Quality of Generic Drug Products         |          | The MHLW established the Expert Committee on Quality of Generic Drug Products (the Expert Committee) in the National Institute of Health Sciences (NIHS) in the Fiscal Year (FY) 2008 to further ensure the reliability of the quality of generic drugs. This section will introduce the details.                                            | 4    |
| 2   | Introduction of the “My Drug List for Safety Update” service     |          | The PMDA provides “My Drug List for Safety Updates” service which can be additionally registered and used for free by the subscribers to PMDA Medi-navi. This section will introduce how to generate the “My Drug List” (registration of drugs) and the tips for convenient functions of this service exclusively for medical professionals. | 8    |
| 3   | Revision of Precautions (No. 287)                                | P        | Riociguat (and 4 others)                                                                                                                                                                                                                                                                                                                     | 16   |
| 4   | List of Products Subject to Early Post-marketing Phase vigilance |          | Lists products subject to Early Post-marketing Phase Vigilance as of July 31, 2017.                                                                                                                                                                                                                                                          | 18   |

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, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

## Abbreviations

|       |                                                       |
|-------|-------------------------------------------------------|
| ADR   | Adverse drug reaction                                 |
| CSV   | Comma separated value                                 |
| DSU   | Drug Safety Updates                                   |
| EPPV  | Early Post-marketing Phase Vigilance                  |
| FY    | Fiscal year                                           |
| JAPIC | Japan Pharmaceutical Information Center               |
| MAH   | Marketing authorization holder                        |
| MHLW  | Ministry of Health, Labour and Welfare                |
| NIHS  | National Institute of Health Sciences                 |
| OTC   | Over-the-counter                                      |
| PMDA  | Pharmaceuticals and Medical Devices Agency            |
| PSEHB | Pharmaceutical Safety and Environmental Health Bureau |
| TEN   | Toxic epidermal necrolysis                            |

# The Expert Committee on Quality of Generic Drug Products

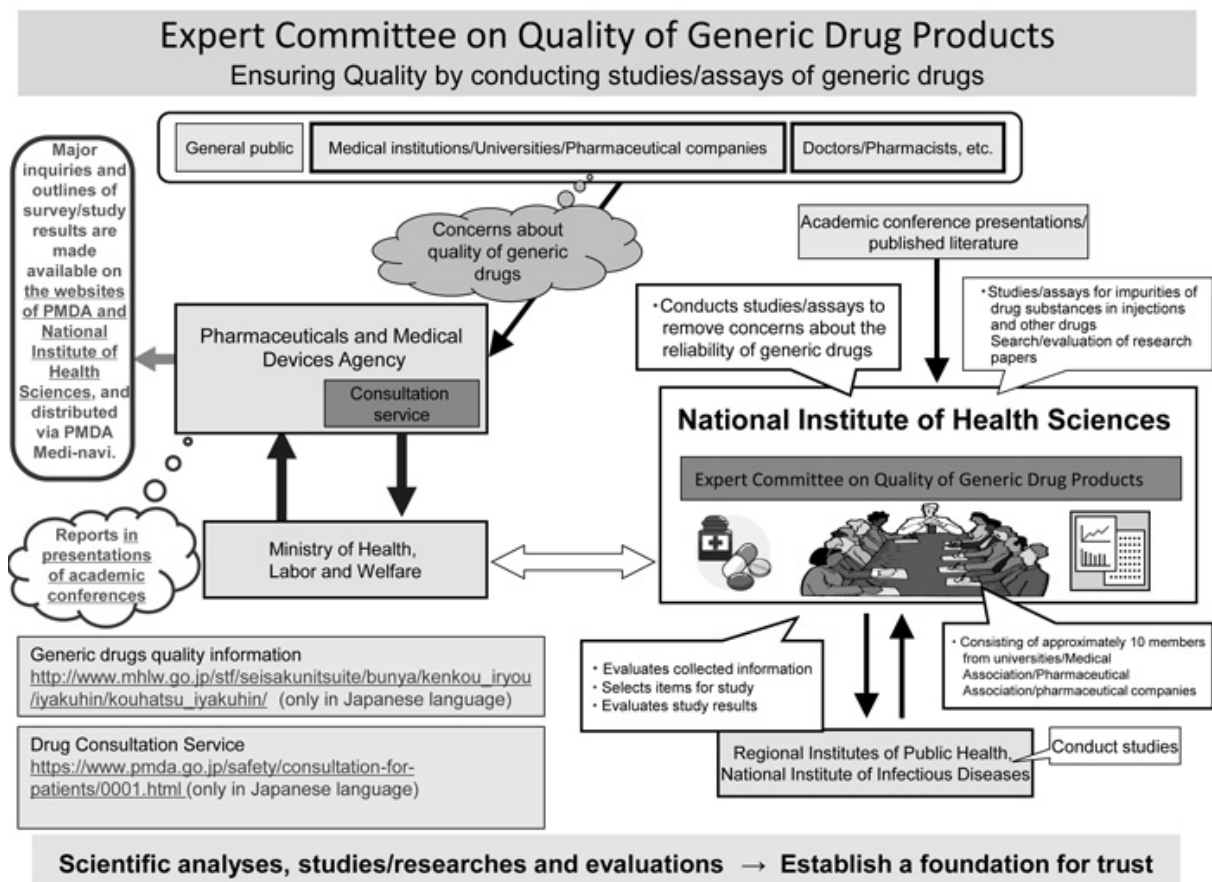
## 1. Overview

The MHLW established the Expert Committee on Quality of Generic Drug Products (the Expert Committee) in the NIHS in the Fiscal Year (FY) 2008 to further ensure the reliability of the quality of generic drugs. The Committee has been called twice a year since then, 18 times in total (as of March 31, 2017), to examine the quality of generic drugs from a scientific viewpoint.

## 2. Activities

The Expert Committee mainly focuses on the review of the following:

- (1) Verification of quality assessment of generic drugs based on their measurements or analyses.
- (2) Scrutiny and evaluation of [1] Published literature or academic conference presentations, [2] Inquiries regarding the quality of generic drugs submitted to the Drug Consultation Service at PMDA and
- (3) Other initiatives for ensuring quality of generic drugs.



(1) Quality assessment of generic drugs based on their measurement or analysis.

In order to ensure an equivalent or higher quality of generic drugs to or than that of their brand name counterparts, the Expert Committee thoroughly analyzes and evaluates products for which quality concern has been raised based on quality-related literature information, drugs with a narrow therapeutic window, and widely used drugs. The Formulation working group consisting of NIHS and the Regional Institutes of Public Health located in 10 prefectures is carrying out the measurement and analysis of the dissolution and purity as follows:

[1] Evaluation of dissolution

This compares the dissolution profile between a generic drug and the reference preparation (the brand name products or the Japanese Pharmacopoeia Reference Standards) in oral solid dosage forms in order to prevent significant non-bioequivalence to the reference preparation. The dissolution profile is measured using 4 pH-indicator test solutions (pH1.2, 3~5, 5.5~7.5 and water) which are comparable to the pH in the gastrointestinal tract. Then the comparability is evaluated as specified in the Guideline for Bioequivalence studies of Generic Drugs.

The Expert Committee has conducted the dissolution study for 1 056 products with 73 ingredients including antihypertensives, antidiabetic agents, anxiolytics/hypnotics, and psychotropics. Of those, 1 brand name drug and 1 generic drug were subjected to recall due to deviation from the approved specifications. Forty-five (45) generic drugs with 23 ingredients did not show the similar dissolution profile range as the brand name drugs even though they met the specification requirements for approval of dissolution and the efficacy and safety of the drug products were confirmed.

If generic drug products fail to demonstrate comparability with their brand name counterparts in dissolution profile, the Expert Committee requests their marketing authorization holders (MAH) to investigate the causes and future measures. For drugs for which measures have been taken to improve their dissolution profile, verification of the dissolution profile is subsequently conducted by the preparation study working group.

[2] Evaluation of purity

Of qualities of generic drugs, purity of injections is very much of concern to medical professionals. Thus, the Expert Committee has conducted the purity test for 113 formulations of 13 ingredients.

Differences among formulations were reported in the incidence of renal disorder following the use of cisplatin injection products in the past, and the issue was discussed in the Committee on Drug Safety, Pharmaceutical Affairs and Food Sanitation Council. Then the Expert Committee decided to conduct purity tests in its 5th meeting and reported the results in its 7th meeting. No significant difference was found in impurities of the related substances among the 6 preparations including brand name drugs in the purity assessment conducted under 3 different conditions.

Meanwhile, 2 of the 10 ritodrine hydrochloride injection products were reported in the 2nd Expert Committee meeting to have contained a higher amount of impurities than the remaining 8 products though the amounts were within the scope of specification requirements for approval. The MAHs investigated the causes and solutions. As a result, reduction in impurities of the products was reported in the 11th Expert Committee meeting.

(2) Scrutiny and evaluation of academic conference presentation or published literature, and inquiries received at PMDA

[1] Academic conference presentation or published literature

The Japan Generic Medicines Association investigates and compiles literature and academic conference reports related to the quality and clinical use of generic drugs which are listed in the pharmaceutical information database at the Japan Pharmaceutical Information Center (JAPIC). The contents of these reports are examined in the Expert Committee meeting. Approximately 40 reports for half a year are reviewed at once in a meeting. Some of the reviewed literature and academic conference reports lack scientific validity or rationale, or include incidents where the Expert Committee cannot determine whether the product is responsible for the issue. In this context, the Expert Committee arguably plays an important role in performing professional evaluations.

[2] Inquiries received at PMDA

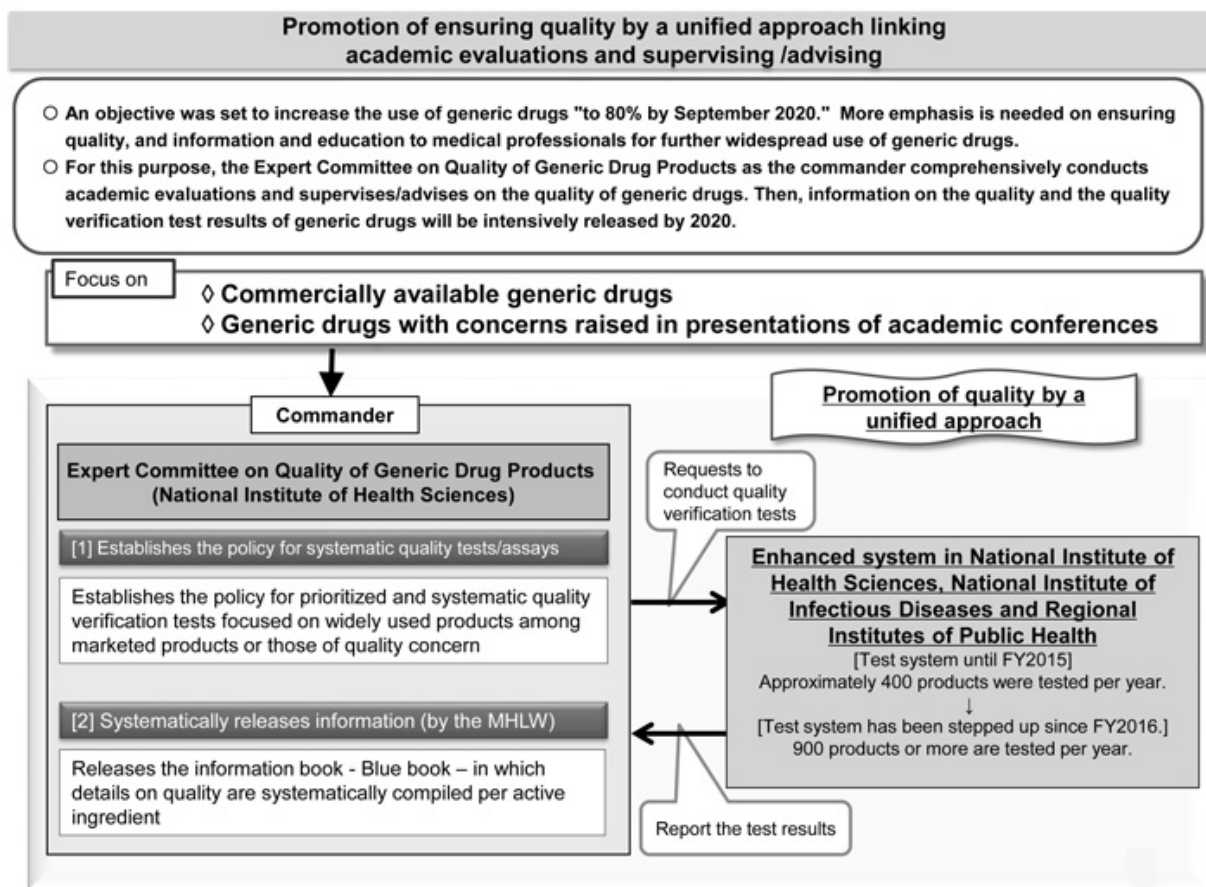
Of the inquiries made by consumers or medical professionals to the consultation service for pharmaceuticals and medical devices (the Drug Consultation Service) in PMDA, particularly those related to quality concerns are subject to detailed investigation. The Expert Committee seeks opinions from the MAH and proceeds with such an investigation.

For both [1] and [2], any issues that the Expert Committee has reviewed and decided require scrutiny of the preparations. They are individually addressed; some will be also examined by the preparation study working group for example.

### 3. Initiatives since Fiscal Year 2016

The MHLW developed the “Comprehensive Drug Industry Reinforcement Strategy ~ Drug discovery with a view to global expansion ~” in September, 2015. To ensure quality of generic drugs, the strategy has proposed an initiative "to enhance a unified approach to ensure quality of generic drugs that links conducting studies or assays to ensure quality of marketed products and accelerating academic evaluations primarily performed by the Expert Committee on Quality of Generic Drug Products, and to release to medical institutions and pharmacies the information which has been systematically compiled with data on quality sorted by active ingredient".

The initiative has been underway since FY 2016 and the concrete actions for this are to establish the policy for prioritized and systematic quality tests focused on widely used products among marketed products or those of quality concern identified by the Expert Committee, then to conduct the quality test for these products at NIHS, the National Institute of Infectious Diseases, and the Regional Institutes of Public Health. On the basis of the test results, information on the quality and the quality test results of generic drugs sorted by active ingredient are systematically compiled in a datasheet (Blue Book), which will be intensively prepared and released by 2020.





## 4. Conclusion

The Basic Policy on Economic and Fiscal Management and Reform 2017, which was approved in the cabinet meeting in June 2017, set an objective "to increase the use of generic drugs to 80% by September 2020." The use of generic drugs has been rapidly expanding with an increasing demand for improved quality of generic drugs, information service to medical professionals, and understanding among the public.

The Expert Committee and other relevant bodies are striving for ensuring quality of generic drugs. Information on the initiatives is widely released not only on the review council website of the NIHS but also via PMDA Medi-navi, the Generic Drugs Quality Information (issued by the Pharmaceutical Evaluation Division, PSEHB, MHLW), and others.

We will continue engaging in those activities in order to gain trust in generic drugs from the public as well as medical professionals.

## 5. References

- The Expert Committee on Quality of Generic Drug  
<http://www.nihs.go.jp/drug/ecgaged.html> (only available in Japanese language)
- Blue book data sheet list  
<http://www.nihs.go.jp/drug/ecgaged/bluebook/list.html> (only available in Japanese language)
- Blue book linked data base (operated by JAPIC)  
<http://www.bbdb.jp/generic/toppage.aspx> (only available in Japanese language)
- Generic Drugs Quality Information  
[http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou\\_iryuu/iyakuhin/kouhatsu\\_iyakuhin/](http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryuu/iyakuhin/kouhatsu_iyakuhin/)  
(only available in Japanese language)

## Introduction of the “My Drug List for Safety Updates” Service

The PMDA provides the “My Drug List for Safety Updates” service, which can be additionally registered and used for free by the subscribers to PMDA Medi-navi (Pharmaceuticals and Medical Devices Information E-mail Alert Service). This service is helpful to manage and browse the updated information of the package inserts if you have registered in advance the products for which you need information.

In view of these answers, this section will provide information about My Drug List for Safety Updates and introduce how to generate your My Drug List (drug registration) and some useful functions which will be of benefit to medical professionals.

### 1. Overview of the “My Drug List for Safety Updates” Service

With the My Drug List for Safety Updates service, it is possible to create a list of drug products for each e-mail address registered for PMDA Medi-navi. For example, users can limit notifications they receive only to specific products, such as drugs used in their hospital ward or drugs handled by their pharmacy, and also easily access the latest information regarding these products, not only package insert information, but also previously issued alert such as Blue Letters (formally-called Rapid Safety Communications), and revision of precautions of package inserts. All of this information can be managed in a single operation and can be reached easily from users' personalized lists. In addition, users will be notified via e-mail when new safety information or updated package insert information regarding the user's registered products is released (See 4. below). By taking advantage of the My Drug List for Safety Updates service, we believe that users working in environments such as hospital wards and pharmacies can have more complete and efficient access to the drug information most critical to their activities.

Please note that the My Drug List for Safety Updates service is only available in Japanese language.

### 2. User Registration

First, we explain the process by which you can register for the My Drug List for Safety Updates service. If you are not already subscribed to PMDA Medi-navi, please do so<sup>1</sup> first.

<sup>1</sup> You may subscribe to PMDA Medi-navi by clicking the pink “New Registration” button on the PMDA Medi-navi top page:(URL: <http://www.pmda.go.jp/safety/info-services/Medi-navi/0007.html>) (only in Japanese language). (Figure 1-(2)).

- (1) Search by “My Drug List” or click on “Use My Drug List for Safety Updates service” on the PMDA Medi-navi top page (Figure 1-(3), Step 1 in Figure 2).
- (2) Click the “Go to registration screen for My Drug List for Safety Updates” button, read and agree to the terms of use, and enter the e-mail address you used to subscribe to PMDA Medi-navi (Step 2 in Figure 2).
- (3) Access the link provided in the confirmation message sent to the e-mail address entered previously, and set your password.  
If you have already set up a password with PMDA Medi-navi, this will be a common password.
- (4) Complete your registration (Step 3 in Figure 2)

After registering, click “To Login Screen” in the window marked with (1), and enter your e-mail address and password when logging in to My Drug List for Safety Update service.



Figure 1 Registration page for the PMDA Medi-navi “My Drug List for Safety Updates” service  
PMDA website top page PMDA Medi-navi top page



Figure 2 Procedure for registering drug products in the “My Drug List for Safety Updates” service



### 3. Registering drug products

Drugs for which you would like to receive information can be registered in either of the following two ways:

- (1) Registration using the non-proprietary or branded name search.  
Enter and retrieve the generic or branded names of the desired drug products on the drug name registration screen and register.
  - [1] Click the “Add drugs for registration” button on the drug name registration screen. The system will display the registration screen (Figure 3-[1]).
  - [2] Enter the generic or branded name(s), select the condition(s) and click the “Search” button (Figure 3-[2]).
  - [3] Put a check in the checkbox of drugs which you need among your registration candidates in the list, and click the “Registration” button (Figure 3-[3]).

Figure 3. Registration using the generic or branded drug name search function

**[1]** Click "Add a drug for registration" button

**[2]** Select the condition (s)  
Click the "Search" button

**[3]** Click the "Registration" button  
Check the correct box

| 薬品コード                               | 販売名                  | 一般名    | 製造販売業者名等                |
|-------------------------------------|----------------------|--------|-------------------------|
| <input checked="" type="checkbox"/> | ○◇錠5mg               | ○◇◇塩酸塩 | 製造販売元/○◇株式会社 販売元/○◇株式会社 |
| <input type="checkbox"/>            | ○○錠10mg              | ○○○    | 製造販売元/○○株式会社 販売元/○○株式会社 |
| <input type="checkbox"/>            | 100000001003 △△錠0.2% | △△△塩酸塩 | 製造販売元/△△株式会社 販売元/△△株式会社 |

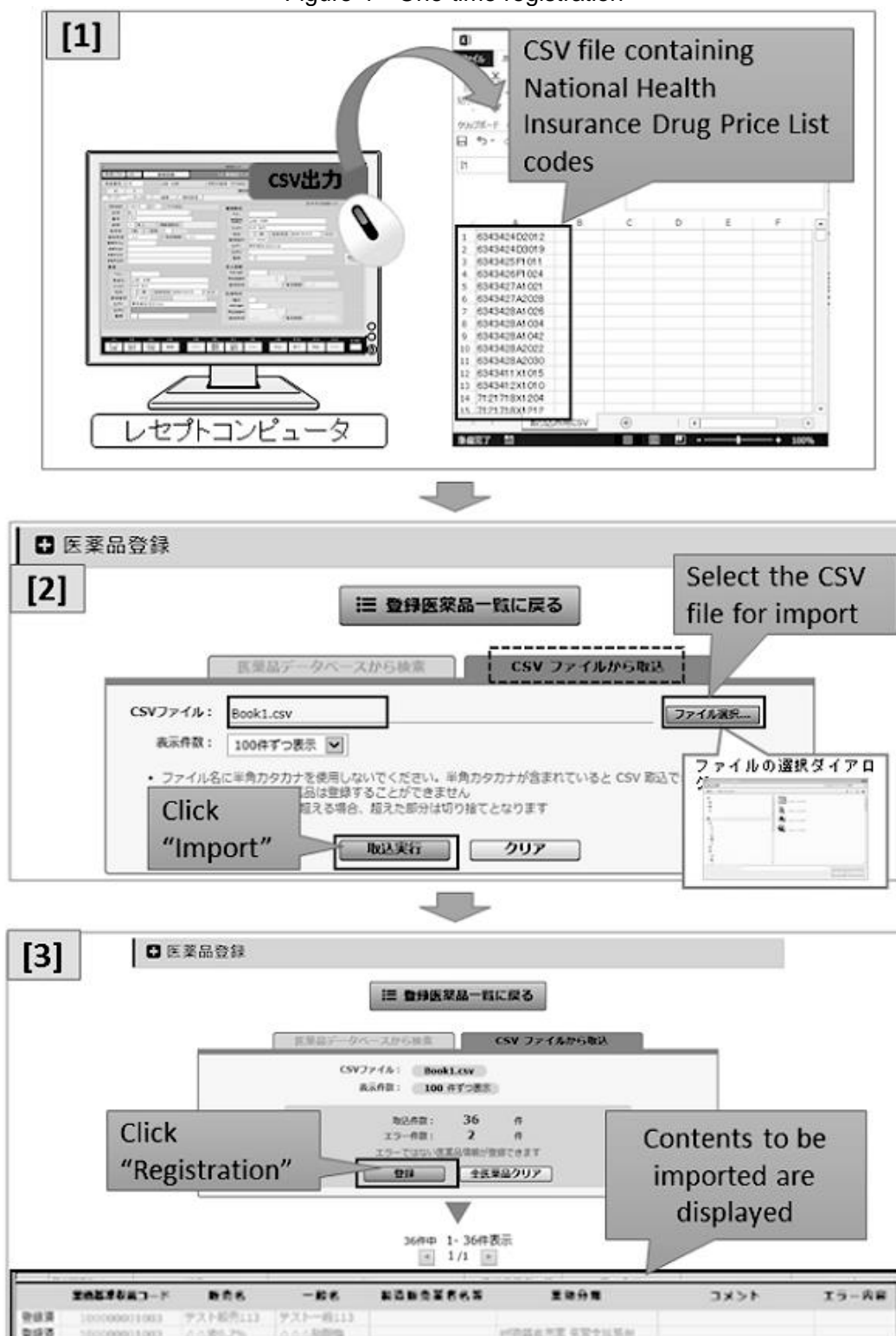
(2) Registration using the codes of the National Health Insurance drug price list [import the file in CSV (Comma separated value) format].

This is a way of registration by importing the file in CSV format, which contains the code of the National Health Insurance drug prices, so that you can register more than one drug at a time. This

way is recommended for hospitals and pharmacies which handle a large number of drugs and cannot afford to register drugs one by one.

- [1] Prepare the CSV file in which the code of the National Health Insurance drug price list has already been imported from the receipt computer or other sources (Figure 4-[1]).
- [2] Click the “Select file” in the “Import from CSV file” tab, select the target CSV file, and click “Import” (Figure 4-[2]).
- [3] Click the “Registration” button (Figure 4-[3]).

Figure 4 One-time registration



## 4. Summary of functions

(1) Browse information on registered drugs

[1] You can find every update in a list regarding package inserts, drug interview forms, drug guide for patients and the manuals for management of individual serious adverse drug reactions (ADRs) (Figure 5-[1]).

[2] A user-friendly icon will inform you of Yellow Letters (formally-called Dear Healthcare Professional Letters)/Blue Letters, revision instruction notices in package inserts or recall information class I when they are issued. Click the icon and you can access the details (Figure 5-[2]).

[3] The history of released information is available for blue letters (Figure 5-[3]).

If you need to handle a large number of drugs and the list for your registered drugs extends beyond one page, you can add to “My Favorite” the drugs which are most frequently used among those registered, for your convenience. (Figure 5-[4]).

Figure 5 Viewing your registered product list

The screenshot displays the 'マイ医薬品集作成サービス' (My Drug Collection Creation Service) interface. At the top, there is a header with the user's email 'username@domain.jp' and a help icon. Below the header, a navigation bar shows '登録医薬品一覧' (Registered Drugs List) with a count of 256 items. A '登録医薬品の追加' (Add Registered Drugs) button is visible. The main content area includes a '表示設定' (Display Settings) section with options for sorting, pagination, and display items. A table of registered drugs is shown, with columns for 'お気に入り' (Favorites), '発出情報' (Distribution Information), 'お問い合わせ先' (Contact Information), '添付文書情報' (Attachment Information), '患者向ガイド' (Patient Guide), '重篤マニユ' (Serious Manual), 'コメント' (Comments), and '製造販売業者名等' (Manufacturer/Marketer Name, etc.). A 'CSV出力' (CSV Export) button is located at the bottom right. Four callouts provide detailed explanations of specific features: [1] A 'NEW!' icon in the '添付文書情報' column indicates new safety information. [2] A star icon in the 'お気に入り' column allows adding drugs to a 'My Favorites' list. [3] A date in the '発出情報' column can be clicked to view details of a Blue Letter. [4] A date in the '発出情報' column can be clicked to view details of a Blue Letter.

(1-1) The display of package insert information (Figure 6)

The following signs tell you the status of package inserts of your registered drugs.

- [1] When the package insert information column shows “○”,  
It means that the registered drug has its package insert information on the PMDA website.
- [2] When the package insert information column shows “—”,  
It means that the registered drug does not have its package insert information on the PMDA website. In this case, a “No package insert information” icon is shown in red with the display’s background in gray. If the package insert is posted on the PMDA website, the link to the information webpage will be created on the next day.
- [3] When the package insert information column shows “Deleted”,  
It means that the previously posted package insert information has been deleted due to change of MAHs (transfer of marketing authorization) or discontinuation of the product. In this case, a “Package insert information deleted” icon is shown in red in the brand name column. You need to check the drug with this icon on the PMDA website and register it again on the drug registration screen in My Drug List for Safety Updates when required. A new function is planned that sends notices to subscribers’ registered e-mail addresses when the package insert of a registered drug is deleted.
- [4] When the package insert information column shows “NEW”,  
For drugs whose package insert information is revised based on the revision instruction notice, an icon “NEW!” indicating the revision is present in the package insert information column for up to a month after the revision.

Figure 6 Display of package insert information

The screenshot displays the '登録医薬品一覧' (Registered Drugs List) page. At the top, there is a header with '登録医薬品一覧' and '登録件数 118件'. Below the header is a search and filter area with '表示設定' (Display Settings) and '登録医薬品の追加' (Add Registered Drugs). The main content is a table with columns: 'お気に入り' (Favorites), 'お気に入り' (Favorites), 'お気に入り' (Favorites), 'お気に入り' (Favorites), '販売名' (Brand Name), '一般名' (Generic Name), '添付文書情報' (Package Insert Information), 'IF' (Information Flag), and '患者向ガイド' (Patient Guide). The first row shows 'AAA液' (Brand Name) and '鎮痛去たん配合剤(1)液' (Generic Name). The '添付文書情報' column for this row contains a 'NEW!' mark and the date '2017/07'. A callout box points to this 'NEW!' mark with the text 'NEW! mark'. The table also shows other drugs like 'メトクロプラミド錠' and 'クリソチニブカプセル'. A 'CSV出力' button is located at the top right of the table area.

(1-2) Comparison between old and new package inserts

You can review the differences between old and new package inserts in a list on the website when updated. Note that the items subject to notification\*2 only will be highlighted by the specific icons and background colors (Figure 7).

\*2 The following items listed in the package insert which need to be notified in accordance with the laws for the quality of pharmaceuticals and medical devices and the efficacy and safety control

- Name
- Precautions in use and handling of the product

[1] For sections which contain some revisions

When some items have been revised in the section, the column is displayed in light blue with a “Revised” icon.

[2] For sections which contain some additional item(s)

When some items have been added in the section, the column is displayed in yellow with an “Added” icon.

[3] For sections which contain some deleted item(s)

When some items have been deleted in the section, the column is displayed in pink with a “Deleted” icon.

Figure 7 Comparison of old and new package inserts (example of revision highlighting)

マイ医薬品集作成サービス：添付文書情報

ABC液 処方せん医薬品

ダウンロード 副作用関連情報 重篤副作用疾患別対応マニュアル 改訂指示反映履歴

旧版と比較する

比較対象： 第5版 (2015年3月改訂)

新旧比較表示の対象となるのは、2014年11月25日（薬事法改正の施行日）以降に届出された添付文書のみとなります

表示方法： 全項目を表示する | 届出対象項目のみ表示する | 表示項目を選択する

PDF表示： PDF出力

| 旧版<br>第5版 (2015年3月改訂)                                                                                       | 最新版<br>第6版 (2015年8月改訂)                                                                                                                |
|-------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| <b>作成又は改訂年月</b> <ul style="list-style-type: none"><li>• 2015年3月改訂 (第5版)</li><li>• 2014年9月改訂 (第4版)</li></ul> | <b>作成又は改訂年月</b> <ul style="list-style-type: none"><li>• 2015年8月改訂 (第6版)</li><li>• 2015年3月改訂 (第5版)</li><li>• 2014年9月改訂 (第4版)</li></ul> |
| <b>日本標準商品分類番号</b><br>871329                                                                                 | <b>日本標準商品分類番号</b><br>871329                                                                                                           |
| <b>日本標準商品分類番号等</b><br>国際誕生年月 2007年4月                                                                        | <b>日本標準商品分類番号等</b><br>国際誕生年月 2007年4月                                                                                                  |
| <b>薬効分類名</b><br>定量噴霧式アレルギー性鼻炎治療剤                                                                            | <b>薬効分類名</b><br>定量噴霧式アレルギー性鼻炎治療剤                                                                                                      |
| <b>承認等</b>                                                                                                  | <b>承認等</b>                                                                                                                            |
| <b>販売名</b><br>ABC液                                                                                          | <b>販売名</b><br>ABC液 XXX <span style="background-color: #e0f0ff;">変更</span>                                                             |
| <b>販売名コード</b><br>123456789012                                                                               | <b>販売名コード</b><br>123456789012                                                                                                         |



(2) A function to send an e-mail to notify the subscribers of various updates on the registered drugs  
The system will send you a notice by e-mail if you need it when the registered package insert information has been revised and when the safety information has been posted on the PMDA website.

[1] Notification service by e-mail on updated package insert information

This service provides you once a day with the information on package inserts when they are updated the previous day. Scope of the updated information can be selected from the following two:

- Entire information on updated package inserts, or
- Items subject to notification only extracted from the above

Of note, this function sends e-mails when updates have been made not only for the package insert information itself but also for the descriptions edited by the MAH. The year and the month listed on the registered drug list screen are the year and the month when the e-mail was sent (“month updated”), not “month revised”, which is stated on the package insert. Be aware that the e-mail-sent date may be different from the revision date. The highlights for revised items on the webpages (1-2) are only applied to the items subject to notification.

[2] Notification of safety information by e-mail

This service provides you once a day with the safety information for the previous day on the registered drug when the following was posted on the PMDA website.

- Risk Management Plan
- Information on the risks of pharmaceuticals under evaluation
- Pharmaceuticals and Medical Devices Safety Information (issued by the MHLW)
- Drug Safety Updates (DSU)

Note that when you receive the items above via PMDA Medi-navi, no notification is sent to you to avoid duplication. The notice only includes the brand-name drugs listed in “Important Safety Information” and “Revision of Precautions” for Pharmaceuticals and Medical Devices Safety Information (issued by the MHLW) and the brand-name drugs listed in “Most Important” and “Others” for DSU.

## 5. Summary

As introduced above, My Drug List for Safety Update service is a very helpful function where you can manage the updates on your own necessary drugs. The PMDA will continue striving for better and user-friendly services.

### Notice concerning PMDA Medi-navi

We started to send mails for the OTC (Over-the-counter) DSU (OTC medicines, information on revision of precautions) via PMDA Medi-navi in July 2017. Review your own subscribed information and if you want, put a check in the checkbox on the “OTC DSU (OTC medicines, information on revision of precautions)” for the mailing service on the registered contents update screen.

## Revision of Precautions (No. 287)

This section presents details of revisions to the Precautions section of package inserts and brand names of drugs in accordance with the Notifications dated August 3, 2017.

1

Cardiovascular agents-Miscellaneous

### Riociguat

|                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Brand name</b>            | Adempas Tablets 0.5 mg, 1.0 mg, 2.5 mg (Bayer Yakuhin, Ltd.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Important Precautions</b> | <u>In a multiregional study in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonias, increased incidences of serious adverse events or fatal outcomes were observed in patients receiving this drug compared with patients receiving placebo. For patients with pulmonary arterial hypertension associated with interstitial pneumopathy, the risks and benefits should be considered in advance by means such as consulting with a physician versed in the treatment of interstitial lung disease and a careful decision on administration should be made.</u> |

2

Anticoagulants

### Warfarin potassium

|                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Brand name</b>                                                   | Warfarin Tablets 0.5 mg, 1 mg, 5 mg, Warfarin Granules 0.2% (Eisai Co., Ltd.), and the others.                                                                                                                                                                                                                                                                                                                                                      |
| <b>Adverse reactions (clinically significant adverse reactions)</b> | <u>Calciphylaxis: Calciphylaxis, which is characterized by painful skin ulceration surrounded with painful purpura as well as calcification of small to medium arteries of subcutaneous adipose tissues or dermis may occur and could lead to sepsis in some cases. Patients should be carefully monitored and if such abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be taken.</u> |

3

Acting mainly on gram-positive bacteria and mycoplasma

### Azithromycin hydrate (tablets, capsules for pediatric use, granules for pediatric use, injections)

|                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|---------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Brand name</b>                                                   | Zithromax Tablets 250 mg, 600 mg, Zithromax Capsules for Pediatric Use 100 mg, Zithromax Fine Granules for Pediatric Use 10%, Zithromax Intravenous Use 500 mg (Pfizer Japan Inc.), and the others.                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Adverse reactions (clinically significant adverse reactions)</b> | <u>Toxic epidermal necrolysis (TEN), mucocutaneous-ocular syndrome (Stevens-Johnson syndrome), and acute generalized exanthematous pustulosis: TEN, mucocutaneous-ocular syndrome, acute generalized exanthematous pustulosis may occur. If any abnormalities are observed, administration should be discontinued and appropriate measures including the administration of adrenal corticosteroid should be taken. These adverse reactions have occurred during administration of the drug or within one week after the end of administration. Careful attention should be paid after the end of administration as well.</u> |

4

Acting mainly on gram-positive bacteria and mycoplasma

## Azithromycin hydrate

|                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Brand name</b>                                                   | Zithromax SR Dry Syrup 2g (Pfizer Japan Inc.)                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Adverse reactions (clinically significant adverse reactions)</b> | TEN, mucocutaneous-ocular syndrome (Stevens-Johnson syndrome), and acute generalized exanthematous pustulosis: TEN, mucocutaneous-ocular syndrome, acute generalized exanthematous pustulosis may occur. If any abnormalities are observed, appropriate measures including the administration of adrenal corticosteroid should be taken. These adverse reactions have occurred within one week after the end of administration. Careful attention should be paid after the end of administration as well. |

5

Antivirals

## Laninamivir octanoate hydrate

|                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Brand name</b>                                                   | Inavir Dry Powder Inhaler 20 mg (Daiichi Sankyo Company, Limited)                                                                                                                                                                                                                                                                                                                                   |
| <b>Important Precautions</b>                                        | Respiratory tract hypersensitivity may increase due to influenza virus infection. Cases of bronchial spasm and decreased respiratory function after administration of <u>this product</u> have been reported. Careful monitoring is necessary when this product is administered to patients with chronic respiratory diseases including bronchial asthma and chronic obstructive pulmonary disease. |
| <b>Adverse reactions (clinically significant adverse reactions)</b> | <u>Bronchial spasm, dyspnoea: Careful monitoring should be performed because bronchial spasm and dyspnoea may occur. If any abnormalities are observed, appropriate measures should be taken.</u>                                                                                                                                                                                                   |

## List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for new drugs refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. It is imposed that its MAH is responsible for collecting ADR from all of the medical institutions where the drugs are used and taking safety measures. The aim of the EPPV is to promote the rational proper use of drugs in medical treatments, and to promptly take actions for prevention of the serious ADR. EPPV is specified as a condition of approval.

(As of July 31, 2017)

⊙: Products for which EPPV was initiated after July 1, 2017

| Nonproprietary name |                                                                                                                                                     | Name of the MAH                                   | Date of EPPV initiate |
|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|-----------------------|
| Brand name          |                                                                                                                                                     |                                                   |                       |
| ⊙                   | Clobetasol Propionate<br>Comclo Shampoo 0.05%                                                                                                       | Maruho Co., Ltd.                                  | July 11, 2017         |
| ⊙                   | Denosumab (Genetical Recombination) <sup>*1</sup><br>Pralia Subcutaneous Injection 60 mg Syringe                                                    | Daiichi Sankyo Company, Limited                   | July 3, 2017          |
| ⊙                   | Fluvoxamine Maleate<br>(1) Luvox Tablets 25 mg, 50 mg, 75 mg<br>(2) Depromel Tablets 25 mg, 50 mg, 75 mg                                            | (1) AbbVie GK<br>(2) Meiji Seika Pharma Co., Ltd. | July 3, 2017          |
|                     | Hydromorphone Hydrochloride<br>Narurapid Tablets 1 mg, 2 mg, 4 mg,<br>Narusus Tablets 2 mg, 6 mg, 12 mg, 24 mg                                      | Daiichi Sankyo Propharma Co., Ltd.                | June 19, 2017         |
|                     | Naldemedine Tosilate<br>Symproic Tablets 0.2 mg                                                                                                     | Shionogi & Co., Ltd.                              | June 7, 2017          |
|                     | Aflibercept Beta (Genetical Recombination)<br>Zaltrap 100 mg I.V. Infusion, 200 mg I.V. Infusion                                                    | Sanofi K.K.                                       | May 29, 2017          |
|                     | Guanfacine Hydrochloride<br>Intuniv Tablets 1 mg, 3 mg                                                                                              | Shionogi & Co., Ltd.                              | May 26, 2017          |
|                     | Forodesine<br>Mundesine Capsule 100 mg                                                                                                              | Mundipharma K.K.                                  | May 24, 2017          |
|                     | Ixazomib Citrate<br>Ninlaro capsules 2.3 mg, 3 mg, 4 mg                                                                                             | Takeda Pharmaceutical Company Limited             | May 24, 2017          |
|                     | Ustekinumab (Genetical Recombination) <sup>*2</sup><br>(1) Stelara Intravenous Infusion 130 mg,<br>(2) Stelara Subcutaneous Injection 45 mg Syringe | Janssen Pharmaceutical K.K.                       | May 24, 2017          |
|                     | Drospirenone/Ethinylestradiol Betadex <sup>*3</sup><br>YazFlex Combination Tablets                                                                  | Bayer Yakuhin, Ltd.                               | April 21, 2017        |
|                     | Golimumab (Genetical Recombination) <sup>*4</sup><br>Simponi Subcutaneous Injection 50 mg, 100 mg Syringe                                           | Janssen Pharmaceutical K.K.                       | March 30, 2017        |
|                     | Zinc Acetate Dihydrate <sup>*5</sup><br>Nobelzin Capsules 25 mg, 50 mg, Nobelzin Tablets 25 mg, 50 mg                                               | Nobelpharma Co., Ltd.                             | March 24, 2017        |

| Nonproprietary name                                                                                  | Name of the MAH              | Date of EPPV initiate |
|------------------------------------------------------------------------------------------------------|------------------------------|-----------------------|
| Brand name                                                                                           |                              |                       |
| Omalizumab (Genetical Recombination) <sup>*6</sup><br>Xolair for S.C. Injection 75 mg, 150 mg        | Novartis Pharma K.K.         | March 24, 2017        |
| Linaclotide<br>Linzess Tablets 0.25 mg                                                               | Astellas Pharma Inc.         | March 22, 2017        |
| Artemether/Lumefantrine<br>Riamet Combination Tablets                                                | Novartis Pharma K.K.         | March 7, 2017         |
| Triamcinolone Acetonide<br>MaQaid Intravitreal Injection 40 mg                                       | Wakamoto Co., Ltd.           | March 2, 2017         |
| Choriogonadotropin Alfa (Genetical Recombination)<br>Ovidrel Syringe 250 µg                          | Merck Serono Co., Ltd.       | March 1, 2017         |
| Apremilast<br>Otezla Tablets 10 mg, 20 mg, 30 mg                                                     | Celgene K.K.                 | March 1, 2017         |
| Dimethyl Fumarate<br>Tecfidera Capsules 120 mg, 240 mg                                               | Biogen Japan Ltd.            | February 22, 2017     |
| Plerixafor<br>Mozobil Subcutaneous Injection 24 mg                                                   | Sanofi K.K.                  | February 22, 2017     |
| Tenofovir Alafenamide Fumarate<br>Vemlidy Tablets 25 mg                                              | Gilead sciences K.K.         | February 15, 2017     |
| Daclatasvir Hydrochloride / Asunaprevir /<br>Beclabuvir Hydrochloride<br>Ximency Combination Tablets | Bristol-Myers Squibb K.K.    | February 15, 2017     |
| Etelcalcetide Hydrochloride<br>Parsabiv Intravenous Injection for Dialysis 2.5 mg, 5 mg, 10 mg       | ONO Pharmaceutical Co., Ltd. | February 15, 2017     |
| Pembrolizumab (Genetical Recombination)<br>Keytruda Injection 20 mg, 100 mg <sup>*7</sup>            | MSD K.K.                     | February 15, 2017     |
| Pembrolizumab (Genetical Recombination)<br>Keytruda Injection 20 mg, 100 mg <sup>*8</sup>            | MSD K.K.                     | February 15, 2017     |
| Ticagrelor<br>Brilinta Tablets 60 mg, 90 mg                                                          | AstraZeneca K.K.             | February 8, 2017      |

\*1 Suppress progression of bone erosion associated with rheumatoid arthritis

\*2 (1) Induction therapy for moderate to severe active crohn's disease (for use only in patients who have not sufficiently responded to conventional treatments),  
(2) maintenance therapy for moderate to severe active crohn's disease (for use only in patients who have not sufficiently responded to conventional treatments)

\*3 Improvement of pain in endometriosis, dysmenorrhoea

\*4 Improvement and maintenance for moderate to severe ulcerative colitis (for use only in patients who have not sufficiently responded to conventional treatments)

\*5 Hypozincemia

\*6 Idiopathic chronic urticaria (limited to patients who are not adequately responsive to conventional treatments)

\*7 PD-L1-positive, unresectable, advanced or relapsed non-small cell lung cancer

\*8 Radically unresectable malignant melanoma