# DRUG USE INVESTIGATION FOR HIV INFECTION PATIENTS OF MARAVIROC

## - HRD Joint Survey -

## NON-INTERVENTIONAL (NI) STUDY PROTOCOL

**Drug Use-results Survey of Celsentri Tablets 150 mg – HRD Cooperative investigation – Protocol**

## 1. Objectives

To understand the following matters and to examine whether or not a special drug use-results survey and/or postmarketing clinical study is needed:

- Unknown adverse drug reactions (ADRs)
- Occurrence of ADRs under actual conditions of use
- Factors that are likely to affect safety, efficacy and other relevant matters

In addition, effects on immune competence, liver function and the cardiovascular system will be also evaluated as priority investigation items.

## 2. Planned Sample Size of the Survey and Rationale of Determination

Based on an approval condition, the drug use-results survey of Celsentri will be conducted in all patients treated with this drug at survey sites to the extent possible.

For the drug use-results survey implemented as part of the HRD cooperative investigation in which Celsentri is included, however, consideration will be paid by setting the upper limit of the number of patients to be enrolled at sites where there are many survey subjects for eliminating the influence of the present survey on routine medical practice at the sites and maintaining the quality of the survey due to this acute increase in the number of patients. When paying consideration, approximately 40 patients per investigator should be enrolled in the HRD cooperative investigation while taking account of time points for collecting case report forms (CRFs) and for case review by the investigator. If it is necessary of select subjects from all patients, consideration should be given so that there is no arbitrarily bias in efficacy or safety.

## 3. Subjects

The indication of Celsentri is as follows:

CCR5-tropic HIV-1 infection

The subjects of this survey will be patients who are prescribed with Celsentri (including retrospective patients).

## 4. Planned Number of Survey Sites by Medical Department

Institutions with which many physicians with a lot of experience in treatment are affiliated and which have many target patients (27 sites; Appendix 1).

## 5. Methods

A cooperative investigation (HRD cooperative investigation) by companies marketing drugs for the treatment of HIV infection[Note 1)] will be conducted using a common CRF. The implementation of this survey will be outsourced to CMIC PMS Co., Ltd. (hereinafter referred to as the CRO).

For the survey method, a central registration system will be adopted for sequentially understanding and controlling patients who used Celsentri.

In this survey, patient enrollment, input of data in survey items and data verification will be carried out using an Electronic Data Capture (EDC) system on the Internet from April 2009.

Some of the HRD cooperative investigation sites cannot connect to the external network so that the concerned sites shall lend a stand-alone computer (hereinafter referred to as the SPC), of which use is limited to the HRD cooperative investigation, and perform the survey.

5.1 Request for the Survey

(1) Request for the survey to physicians and conclusion of a contract

The CRO should request institutions collaborating in the survey to conduct the survey in writing and conclude a written contract.

(2) Request for the survey at the institutions concluded the contract

The CRO should fully explain physicians at institutions where the contract has been concluded, about the gist of the survey using the outline of the implementation of the HRD cooperative investigation, and given them a user's ID and password for the HRD cooperative investigation.

5.2 Patient Enrollment

(1) For patients who have been on drugs subject to the HRD cooperative investigation at the time of the contract or will start to receive them during the survey period, the investigator/subinvestigator should enter required information (medical record number or identification number, patient's initials [as necessary], gender, birth date [as necessary, age; e.g., age group], pregnancy status, inpatient/outpatient status, name of the drug surveyed and start date of treatment) on the enrollment screen of the EDC system, and send it using the user's ID and password issued for each investigator/subinvestigator. The patients' enrollment numbers will be issued by the EDC system. The sites that cannot connect to the external network should send or collect the data after inputting them in the SPC.

Patients who have been continuously on the drugs subject to the HRD cooperative investigation will be automatically continued to be enrolled based on data of the previous CRFs.

(2) The CRO should, as necessary, report the status of patient enrollment to the applicable companies using an HRD cooperative investigation control chart.

(3) Sites having a markedly high number of patients should first understand an expected number of new patients and then enroll new patients in the order of the re-enrollment of new patients on the day of enrollment in the HRD cooperative investigation among continuing patients and patient verification by the sites. The ratio of the number of re-enrolled continuing patients and newly enrolled patients should be adjusted. Overall, approximately 40 patients per investigator should be enrolled.

5.3 Progress Control of the Drug Use-results Survey

(1) The CRO should be aware of the progress of the survey at the study sites in charge to systematically promote it using the HRD cooperative investigation control chart.

(2) The Postmarketing Surveillance Control Manager should investigate whether or not the HRD cooperative investigation has smoothly progressed and, as necessary, give appropriate instructions to the CRO and relevant departments in the company.

5.4 Data Input/Sending and Reinvestigation

The investigator/subinvestigator should enter results up to the end of March of each year, in principle, between April and July and send them (Data will be collected using a USB memory device at sites where Internet communication is not available.). The CRO should request the investigator to perform a reinvestigation by gathering reinvestigations from each company. The CRO should print out the inputted and corrected CRFs from the EDC system. The investigator should check the contents and sign/seal them. These CRFs should be defined as the originals, and the CRO should send their copies to the applicable companies.

5.5 Statement of Confirmation on All-case Surveillance

The CRO should prepare a statement of confirmation collectively for enrolled patients by investigator and drug. The CRO should bring the statement of confirmation at the time of signing/sealing the originals of the CRFs, and the investigator should sign/seal the statement

of confirmation to ensure that the enrolled patients are all the treated patients. The CRO should send a copy (including fax) of the statement of confirmation signed/sealed by the investigator to the applicable company, and the CRO should retain the original.

5.6 Collection of Safety Information

The "HRD Cooperative investigation: Spontaneous Reporting Form for ADRs, etc." should be distributed to all medical institutions where drugs for the treatment of HIV infection are used to collect safety information from physicians by fax.

(1) At the time when the CRO visits the HRD cooperative investigation sites, safety information should be continuously collected even for patients who completed the patient enrollment period of the drug use-results survey using means such as the "HRD Cooperative investigation: Spontaneous Reporting Form for ADRs, etc."

(2) At institutions other than the HRD cooperative investigation sites, medical representatives (MRs) of each manufacturer should actively collect safety information.

5.7 Handling of Patients with ADRs

(1) When ADRs, etc. (including those for which the causal relationship is unknown) suspected to be caused by the drug occurred, the investigator/subinvestigator should immediately notify them to the CRO or complete required information in the "HRD Cooperative investigation: Spontaneous Reporting Form for ADRs, etc.," which has been provided beforehand, and fax it to the CRO.

(2) When learning the onset of ADRs, etc. (including those for which the causal relationship is unknown) associated with Celsentri from healthcare professionals, an MR should immediately fill out the "HRD Cooperative investigation: Spontaneous Reporting Form for ADRs, etc." and directly fax it to the CRO. When receiving a Spontaneous Reporting Form, it should be immediately faxed to the CRO.

(3) When an anti-HIV infection drug, for which the causal relationship cannot be ruled out, was concomitantly used, an MR should obtain prior consent of the investigator for reporting ADR information to a company related to the concerned drug.

(4) When identifying ADR information in data sent from the investigator, the CRO should notify it to the applicable company.

(5) The applicable company should assess and analyze this ADR information and, as necessary, instruct a detailed investigation to the CRO. The CRO should request the investigator to input and send the latest information using the EDC system and inform it to the applicable company after receiving the said information.

## 6. Planned Period of the Survey

The survey will be started in April 2009. The patient enrollment period will be until the end of the 8th year.

Enrollment period: April 1, 2009 to March 31, 2017

## 7. Investigation Items

7.1 Identification Characteristics of the Investigators/Subinvestigators

Names of the site, department and investigator/subinvestigator, date of completing the form, and patient enrollment number

<HRD cooperative investigation: CRF>

7.2 Patient Background Characteristics

Medical record number, inpatient/outpatient status, patient's initials, birth date, history of HIV infection treatment, race, gender, pregnancy status, infection route, underlying disease, date of

infection, past history, presence or absence of allergy, and presence or absence and details of complications

7.3 Prescribed Anti-HIV Drugs

Name of the drug, daily dose, duration of treatment and treatment continuation/discontinuation status

7.4 Prescribed Concomitant Medications (including drugs for the treatment of HIV-related diseases)

Presence or absence of prescribed concomitant medications, name of the drug, dose, duration of treatment, treatment continuation/discontinuation status and reason for use

7.5 Concomitant Therapies

Presence or absence of concomitant therapies, details of therapy, duration of therapy and reason for therapy

7.6 Patient Outcome (at discontinuation of the survey)

Date of outcome and details of outcome

7.7 HIV-RNA, CD4, CDC Classification, Time-course of Body Weight and Tropism

Date of test, number of HIV-RNA copies, CD4 count, CDC classification, body weight and tropism

7.8 Abnormal Changes in Laboratory Values

(i) Presence or absence of abnormal changes in laboratory values

(ii) Date of test

(iii) Hematology

White blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, differential white blood count, partial thromboplastin time (PTT), activated partial thromboplastin time (APTT), fibrinogen and fibrin degradation products (FDP)

(iv) Blood biochemistry

Total protein, albumin, total bilirubin, aspartate aminotransferase (AST) (glutamic-oxaloacetic transaminase, GOT), alanine aminotransferase (ALT) (glutamic pyruvic transaminase, GPT), lactic dehydrogenase (LDH), alkaline phosphatase (Al-P), gamma glutamyl transpeptidase (γ-GTP), creatine phosphokinase (CPK), blood urea nitrogen (BUN), creatinine, uric acid, total cholesterol, triglyceride, electrolytes, amylase, lipase, fasting blood glucose, C-reactive protein (CRP) and $\beta_2$-microglobulin

(v) Urinalysis

Protein, sugar, occult blood and sediment

(vi) Abnormal ocular findings

7.9 Adverse Events (including ADRs, abnormal changes in laboratory values, new onset of opportunistic infection, etc.)

Presence or absence of adverse events (AEs), date of onset, diagnosis or name of specific symptom, details of symptoms/course and therapeutic action, seriousness, reason for assessing the event as serious, date of outcome, outcome, and relationship between disease and the drug used

(In the case of death) Presence or absence of autopsy, date of autopsy, autopsy findings and examination

7.10 Priority Investigation Items

In this survey, the occurrence of the following items will be defined as the priority investigation items:

(i) Effect on immune competence
[Reason for selection]
Nonclinical or clinical studies of Celsentri have not suggested that Celsentri treatment increases infections, malignancies, etc. However, there is a concern that Celsentri may affect immune competence (onset of infections, malignancies, etc.) based on its mechanism of action to inhibit CCR5 chemokine receptors.
[Investigation method]
By focusing on the onset of AEs such as infections and malignancies, they will be tabulated by the causal relationship with Celsentri and stratified according to patient background characteristics to evaluate the safety of Celsentri.

(ii) Effect on liver function
[Reason for selection]
No clinical data obtained so far shows the effect of Celsentri on liver function compared with placebo. However, a nonclinical study in rats revealed high exposure to the liver. CCI [redacted] Also, a Phase III study of Celsentri (A4001026) reported cases of liver disorder suspected to be related to maraviroc and resulted in liver transplantation.
[Investigation method]
By focusing on the onset of abnormal liver function test values and AEs mainly corresponding to hepatobiliary disorders according to the System Organ Class (SOC) of the MedDRA, they will be tabulated by the causal relationship with Celsentri and stratified according to patient background characteristics to evaluate the safety of Celsentri.

(iii) Effect on the cardiovascular system
[Reason for selection]
Clinical studies and a Phase IIb/III study to evaluate QT prolongation revealed no clinically significant effect on the QTc interval. In addition, the onset of myocardial infarction and ischemic heart disease during Celsentri treatment is rare, and their incidence is the same as that in this population with a history of treatment. However, nonclinical studies suggested that Celsentri might prolong the QT interval at concentrations above the therapeutic concentration.
[Investigation method]
By focusing on AEs mainly corresponding to cardiac disorders according to the SOC of the MedDRA, they will be tabulated by the causal relationship with Celsentri and stratified according to patient background characteristics to evaluate the safety of Celsentri.

A detailed investigation will be separately carried out in patients corresponding to the priority investigation items if the sponsor finds it necessary.

## 8. Analysis Items and Methods

### 8.1 Analysis Sets

The safety analysis set will consist of, in principle, patients who meet the criteria for patients and are confirmed to have received at least one dose of Celsentri. The efficacy analysis set will consist of, in principle, evaluable patients (patients who are determined to be properly assessed) in accordance with a separately specified analysis plan.

### 8.2 Analysis Methods

(1) Analyses related to safety evaluation

In the safety analysis set, the primary analysis items will be the occurrence of common ADRs and the incidence of ADRs (proportion of patients with AEs with which Celsentri's causal

relationship could not be denied). In addition, when tabulating the incidence of ADRs by factor such as patient background characteristics, factors affecting the onset of ADRs will be also examined.

(2) Analyses related to efficacy evaluation

Efficacy parameters for anti-HIV drugs such as a CD4 count, number of HIV-RNA copies and CDC classification will be tabulated and analyzed by patient background characteristic to examine factors affecting the efficacy of Celsentri. In patients tested for tropism, the relationship with the status of tropism change will be also evaluated.

## 9. Organization System for the Implementation of the Survey

The survey will be conducted using the system described in Appendix 3 in accordance with the procedures for the implementation of the HRD cooperative investigation (Appendix 2). The procedures for notifying ADRs, etc. are presented in Appendix 4.

This survey will be performed as a cooperative investigation by companies marketing drugs for the treatment of HIV infection[Note 1)] using a common CRF. The common CRF for the drug use-results survey may be completed one copy for one patient even if a few anti-HIV infection drugs are coadministered during the reexamination period.

## 10. Name and Address of the Contractee, and the Scope of the Concerned Outsourced Activities

(1) Contractee

Address: PPD

Name: PPD , PPD CMIC PMS Co., Ltd.

Name of the person responsible for implementation: PPD , Postmarketing Surveillance Operation Implementation Supervisor

(2) Scope of outsource activities

1) Request to and contract with institutions
2) Issuance of a user's ID and password to each investigator
3) Retention of the originals of enrollment forms
4) Sending the copies of enrollment forms
5) Verification of registration and investigation items entered and sent by the investigators
6) Collection of the originals of CRFs
7) Preparation and collection of the statement of confirmation
8) Sending the copies of CRFs
9) Arranging reinvestigation items
10) Request for a reinvestigation
11) Retention of the originals of CRFs
12) Sending the CRFs (final version)
13) Data locking
14) Coding
15) Data tabulation/analyses

## 11. Other Necessary Matters

(1) Protocol revision

When this drug use-results survey protocol needs to be revised based on new evidence obtained according to the progress of the survey, it should be, as necessary, revised upon discussion with the companies marketing drugs for the treatment of HIV infection participating in the

cooperative investigation. Also, when approval for partial changes in the dosage and administration or indication is granted during the reexamination period (excluding the case where a reexamination period is newly designated), whether or not the protocol needs to be revised should be reviewed, and the protocol should be, as necessary, revised.

(2) Actions in the case where there are problems or questions

In the cases, for example, where the onset of serious and unknown ADRs was suggested, where the incidence of ADRs largely increased, where any efficacy or safety issues are identified compared with pre-approval data, and where the onset of different ADRs was suggested, the conduct of a special drug use-results survey and/or postmarketing clinical study to detect or confirm their causes and validate estimations made from the results of examination should be considered.

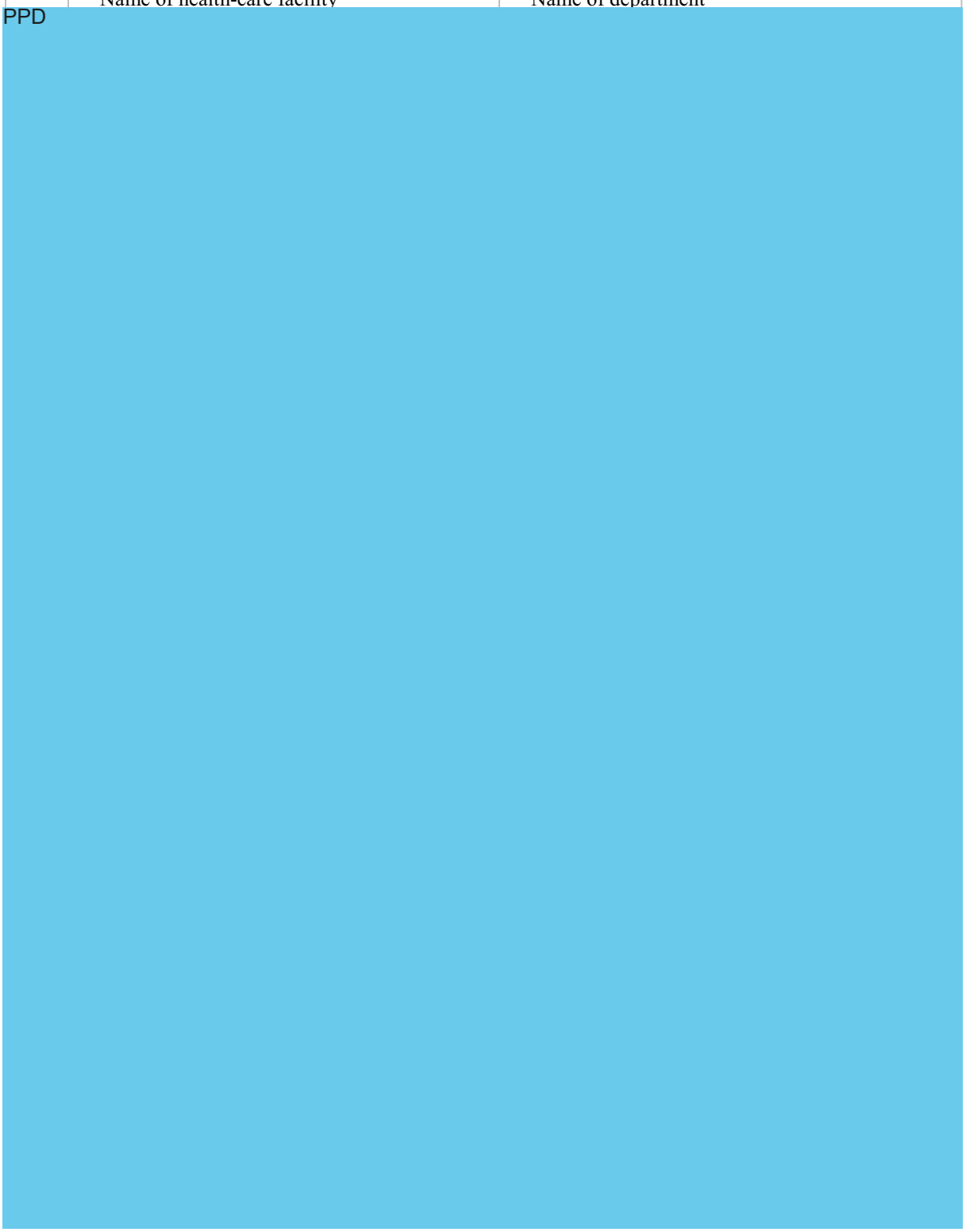
Note 1) Companies that developed drugs for the treatment of HIV infection (in random order); companies participating in the HRD cooperative investigation (as of January, 2014)
ViiV Healthcare K.K.
MSD K.K.
GlaxoSmithKline K.K.
Mitsubishi Tanabe Pharma Corporation
Japan Tobacco Inc.
Pfizer Japan Inc.
Janssen Pharmaceutical K.K.
Bristol-Myers Squibb

Prepared on June 1, 2015

Appendix 1

**Participating health-care facilities：30 (as of March, 2013)**

| | Name of health-care facility | Name of department |
|---|---|---|



Appendix 2

Procedures of the HRD cooperative investigation

**Healthcare facility** **CRO** **Each company**

[CMIC-PMS Co., Ltd.]

FAX: PPD

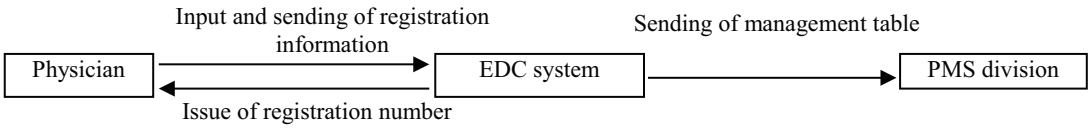
PHONE: PPD

<Request and contract>


[Preparation of table of contract status for each health-care facility]

- Initial password is issued after signing of contract.

<Patient registration>

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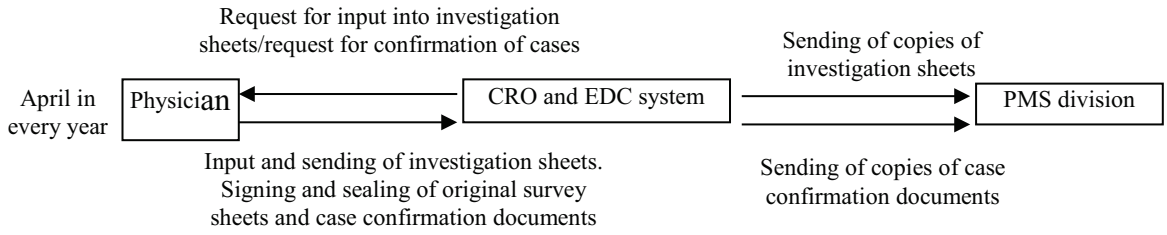
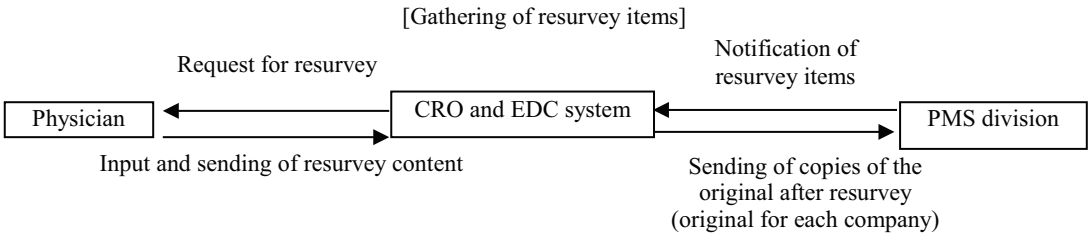



[Storage of original of case confirmation documents]

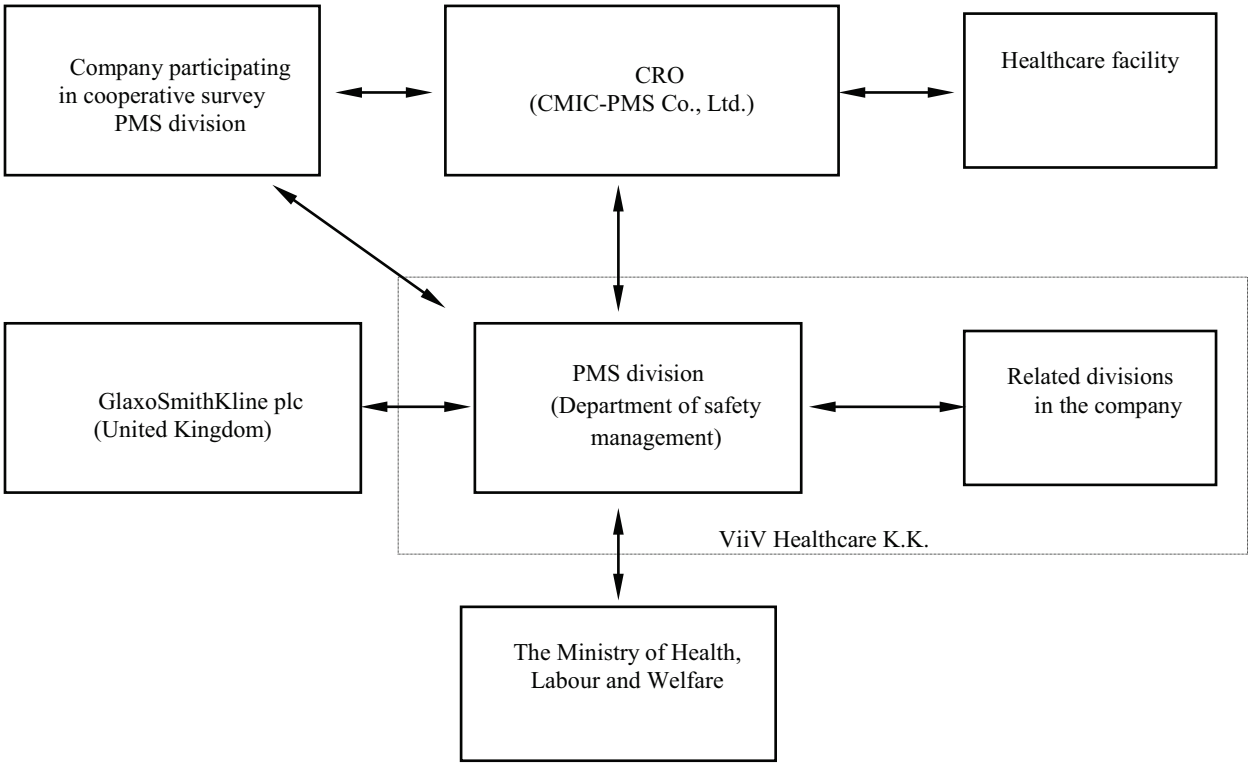
<Resurvey>




[Storage of original survey sheets]

Appendix 3

**Organization for the HRD cooperative investigation**




<Organization for the HRD cooperative investigation>

ViiV Healthcare K.K.

Department in charge of management of post-marketing surveillance, etc. : Department of Safety Management

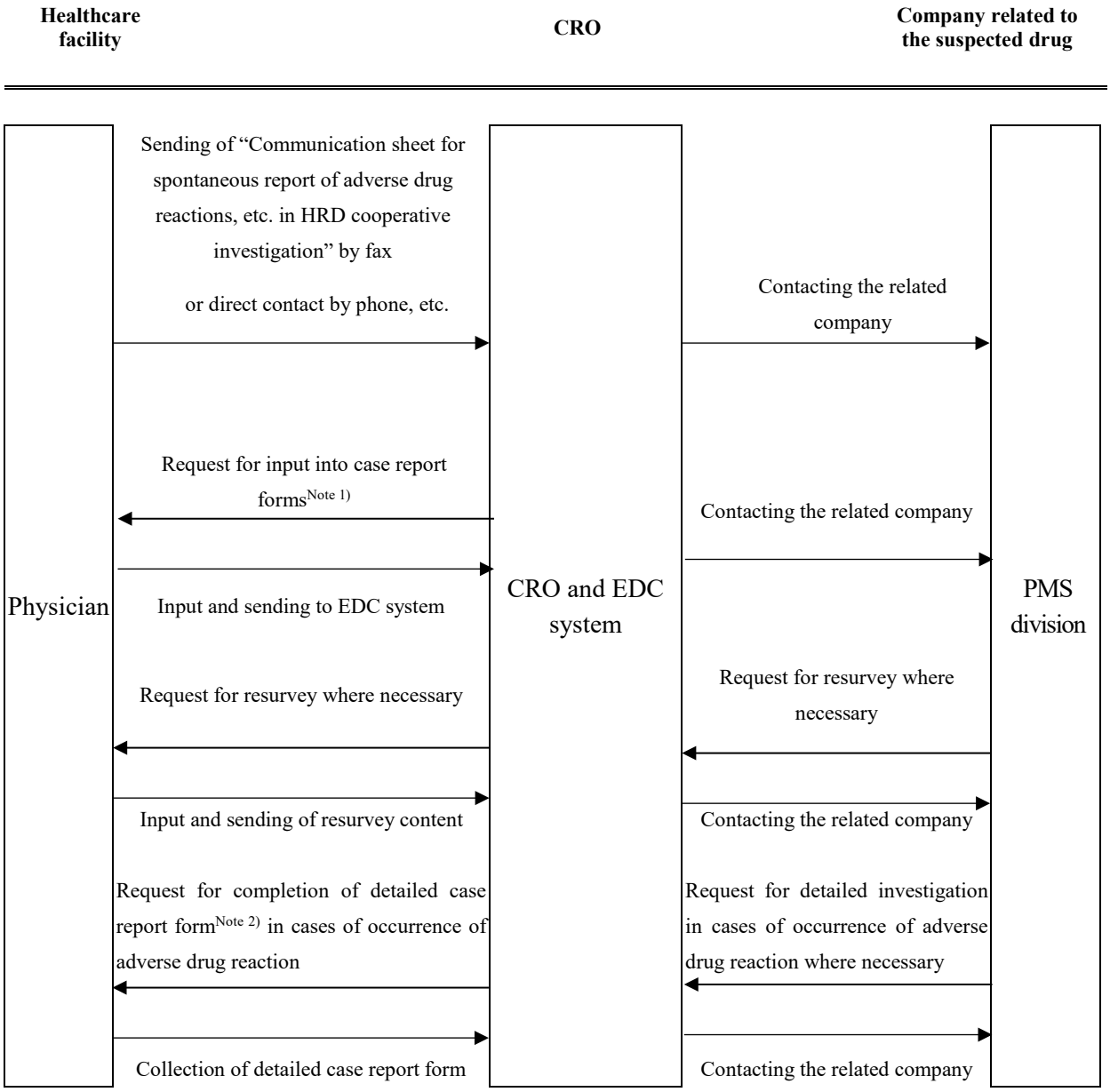
Manager of Post-marketing Surveillance, etc. : PPD, Department of Safety Management

Organization for the HRD cooperative investigation

1) Department of Safety Management at ViiV Healthcare K.K. (hereinafter referred to ViiV Department of Safety Management) shall design and plan the post-marketing surveillance for the application for reexamination jointly with companies participating in the cooperative investigation, commission the CRO (CMIC-PMS Co., Ltd.) to conduct the investigation, manage the status of conduct, instruct to conduct resurvey, evaluate and analyze the information obtained in post-marketing surveillance, take measures based on the evaluation and analysis, prepare Periodic Safety Update Reports and the reexamination application data and report to or file application with the Ministry of Health, Labour and Welfare.
2) ViiV Department of Safety Management shall conduct the investigation in collaboration with the companies participating in the cooperative investigation and the CRO.
3) When requesting for post-marketing surveillance, the CRO (monitor) shall explain the main points of the investigation and the case report form to physicians at health-care professionals, distribute the case report forms and the implementation guideline, manage the progress, collect the case report forms and request for reinvestigation.
4) In order to track the progress of the investigation, the CRO shall prepare the management table for post-marketing surveillance and report the progress periodically to ViiV Department of Safety Management.
5) The person responsible for specific Drug use investigation shall check once a month whether the investigation is proceeding smoothly at the CRO using the management table for post-marketing surveillance, report the result to the manager of post-marketing surveillance and give instructions to the CRO if necessary. If a problem such as delay in progress arises, the person responsible for specific Drug use investigation shall discuss the way of responding to the problem with the companies participating in the cooperative investigation.

Appendix 4

# The procedure of communication regarding adverse drug reactions, etc.




Note 1) EDC system for case report forms for the HRD cooperative investigation
Note 2) Detailed case report form for adverse drug reaction, etc. in the HRD cooperative investigation