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Inspections

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PROCEDURE FOR THE PREPARATION OF A RISK-BASED PROGRAMME FOR ROUTINE PHARMACOVIGILANCE INSPECTIONS OF MAHs CONNECTED WITH HUMAN CENTRALLY AUTHORISED PRODUCTS (CAPs)

Ad Hoc PhV Inspectors Working Group (PhV IWG)

Applies to: EMEA, EU/EEA Inspectorates	
Summary of scope: This SOP provides unified standards on the preparation of a risk-based programme for routine pharmacovigilance inspections of MAHs connected with CAP products.	
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1 INTRODUCTION

According to Regulation (EC) No. 726/2004, the supervisory authorities shall be responsible for verifying on behalf of the Community that the holder of the marketing authorization of the medicinal product for human use or the manufacturer or importer established within the Community satisfies the requirements laid down in Titles, IV, IX and XI of Directive 2001/83/EC for medicinal product for human use.

According to Directive 2001/83/EC the Competent Authority shall ensure, by means of repeated inspections, and if necessary unannounced inspections, that the legal requirements governing medicinal products are complied with. The Competent Authority may inspect the premises, records and documents of Marketing Authorization Holder (MAH) or any firms employed by the MAH to perform the activities described in Title IX and in particular articles 103 and 104.

Competent Authorities at national and EU level need to develop a systematic and risk-based approach to make the best use of their surveillance and enforcement resources whilst maintaining a high level of public health safety. A risk-based approach to inspection planning will enable the frequency, depth and breadth of inspections to be determined accordingly.

According to the Volume 9A, the CHMP, in conjunction with the Competent Authority of the Member State (MS) in whose territory the MAH's QPPV is located and applicable Pharmacovigilance and Inspectors' Working Parties, will determine a programme for inspection in relation to centrally authorised products (CAPs). These inspections will be prioritised based on the potential risk to public health, the nature of the products, extent of use, number of products that the MAH has on the EEA market and other risk factors.

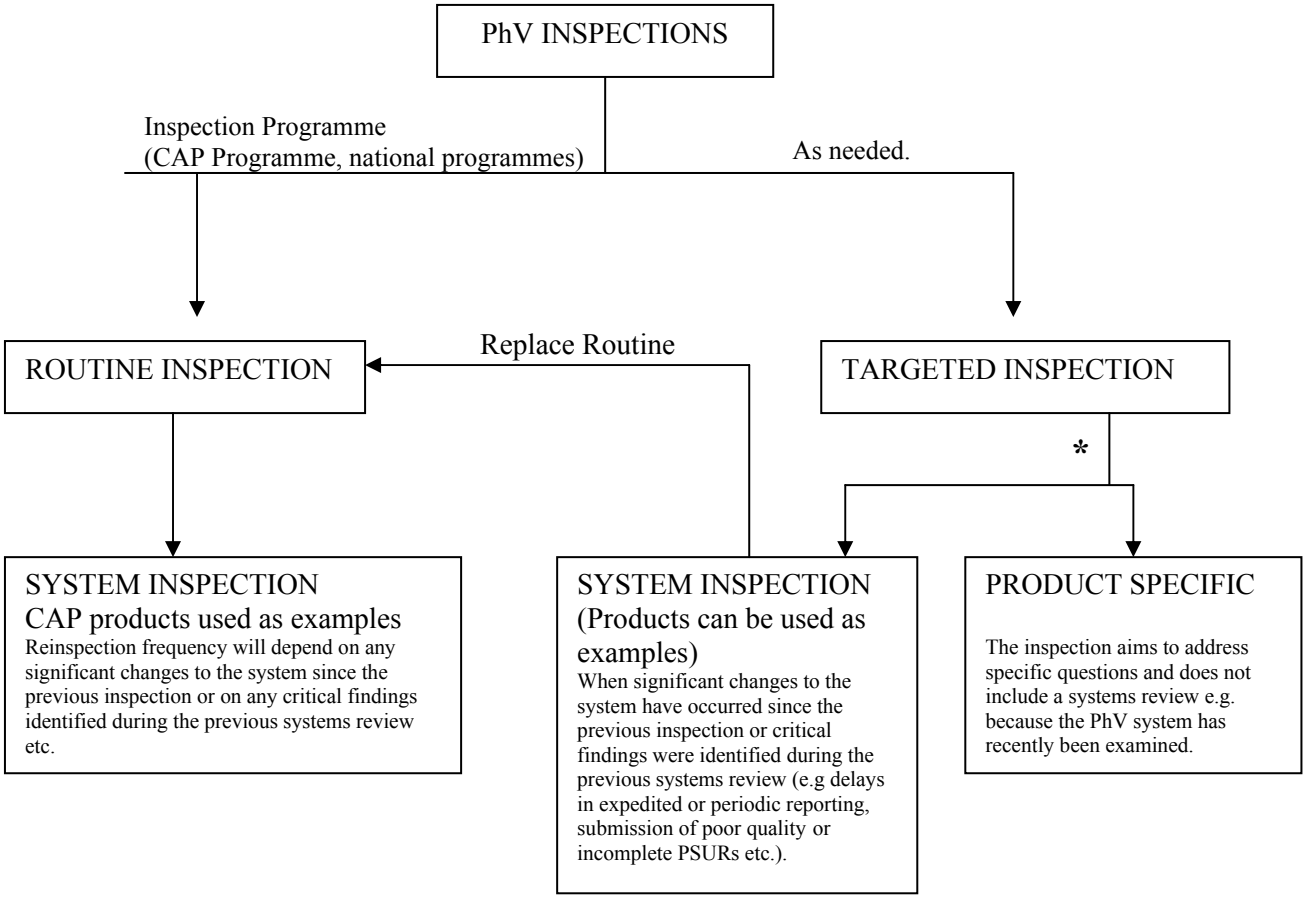
Based on this, a written procedure that covers the preparation, revision, implementation and supervision of an annual inspection programme is needed. This programme should ensure that the extent and frequency of inspections can be adhered to as planned. Sufficient resources must be determined and made available to ensure that the designated programme of inspections can be carried out in an appropriate manner.

In general, it is anticipated that national inspection programmes will fulfil the need for the routine inspections of this programme and therefore it is expected that the programme described in this procedure focused on CAP products will be achieved mainly through the national programmes. However there will be situations where these inspections might be specifically requested by the CHMP (e.g. global PhV sites in third countries). Targeted inspections will also be reflected in this programme as they may replace the need for a routine inspection.

2 PURPOSE

This document outlines the procedure for a risk-based planning and scheduling of routine PhV inspections in relation to CAPs. These inspections will be prioritised based on the potential prioritisation factors identified in annex 1, although considerations should be given to inspection early post authorisation and to introducing a random element to the inspection programme at an early stage.

The programme will be separated from any targeted inspection, but if a targeted inspection has been or will be conducted in a similar timeframe it may replace the planned routine inspection and for this reason it will remain reflected in the programme with a new scheduled year for that inspection. Specific triggers for targeted inspection can be found in annex 2.



* Depending on the context, elements of these may be combined

3 SCOPE

This procedure covers the PhV inspection of MAHs with CAPs. This procedure covers human medicinal products.

It is anticipated that national inspection programmes will fulfil the need for the routine inspections of this programme and, therefore, it is expected that this programme focused on CAP products will be achieved mainly through the national programmes. Therefore, when a Competent Authority has carried out, or intends to carry out an inspection covering the scope of that requested within the required timeframe, this inspection will suffice and its results will be made available to the CHMP or to the applicable reviewing agency.

There will be situations where these inspections might be specifically requested by the CHMP (e.g. global PhV sites in third countries).

The focus of these inspections is to determine whether the MAH has the personnel, systems and facilities in place to meet their regulatory PhV obligations for CAPs in the EEA. These inspections will be requested as system inspections with one or more specific products selected as examples, for which specific information can be traced and verified through the various processes. This shall provide a practical evidence for the functioning of the MAH's PhV system in the Community and their compliance with the regulatory requirements.

The CHMP will request the relevant Competent Authority to carry out and report on an inspection of the PhV system within 4 years after the Commission decision of the first CAP of the MAH. The timing of the first inspection and any further inspection will be determined on the basis of prioritisation criteria described in this procedure but as a principle, re-inspections will take place based on risk assessment criteria. A four year inspection cycle will be used but may be shortened or lengthened based on the risk assessment. This process and the methodology should be revised as appropriatte.

4 PROCEDURE

EMEA Inspection Sector in conjunction with the Ad Hoc PhV Inspectors Working Group (PhV IWG) and the PhV Working Party (PhV WP) will prepare a four-yearly programme of routine PhV inspections that will be revised on a yearly basis. The preparation and revision of this programme will be initiated 12 months in advance of the implementation of the first year of such programme and will cover, apart from the need of changes in the programme, the preparation of the annual programme 4 years ahead which will replace the one under implementation that year and allow for having always a consecutive four-yearly programme (i.e. considering a 2008-2011 programme, during the implementation of the 2008 programme the new 2012 programme should be prepared in order to have the consecutive 2009-2012 four-yearly programme).

This programme will be based on CAPs but as most of these inspections are anticipated to be performed as part of the national programmes, products authorised via the decentralised or mutual recognition procedure may be added as decided at national level or at the request of the PhV WP, whenever the same system is used for these products as well.

The periodicity of re-inspections will be determined by risk factors.

4.1 Gathering information

At least twice per year (1Q and 3Q), EMEA will gather information from the SIAMED database regarding changes in the information currently available in the four-yearly programme (e.g. changes in the location of the QPPV) and also information on any new MAHs with marketed CAPs to be included in the programme.

In addition, previous information available on CAP inspections or inspections conducted/planned at national level will also be taken into consideration (e.g. the re-inspection dates proposed by the inspectors after the conduct of the inspections proposed in this programme) in order to ensure that the scheduled year for an inspection of a particular MAH in this programme fits in with the national ones.

Other necessary tools will be identified and implemented to facilitate the collection and exchange of information on risk factors/triggers for inspections like the “Template for collecting information on PhV issues for the attention of the inspectors/assessors” (annex 3).

4.2 Preparation and revision of the programme

A programme covering a plan of PhV inspections for a rolling four-year cycle will be prepared 12 months in advance of the implementation of the first year of such programme. This preparation includes the preparation of a yearly programme 4 years ahead (which will replace the one under implementation that year and allow for a consecutive four-yearly programme to be in place) and further revisions in order to introduce any necessary changes to the programme.

Therefore, the programme should be a dynamic rolling four-year cycle so will be revised each year to reflect the inspections already performed, the revised priorities and the new MAHs/CAP products joining the system.

EMEA in conjunction with the Ad Hoc PhV IWG and PhV WP will prepare a first four-yearly programme based on the information gathered from SIAMED and on inspections performed. The prioritising of the MAHs to be inspected will be in accordance with the “primary prioritisation factors” in the annex 1. The priority list in this first programme will be in principle established based on the number of prioritisation factors that concur at the same time for a particular MAH. Once a preliminary selection has been made, the “secondary prioritisation factors” (see annex 1),

the conduct of an inspection early post authorisation and/or the introduction of a random element to the inspection programme may be used in order to refine this selection.

The preparation/revision of further four-yearly programmes will take into consideration the following rules:

- For new MAH to be included in the programme, the feedback from the inspectorates on when they plan to inspect these MAHs according to their national programmes will be considered. This proposal may need to change based on the prioritising factors in annex 1. The conduct of an inspection early post authorisation and/or the introduction of a random element to the inspection programme may be used as well to refine the selection.

- For the MAHs already included in the programme, the inspectorates will be asked to confirm whether or not a change is needed, ensuring that these CAP inspections fit in with their national programmes. EMEA may consider requesting the inspection of a particular MAH in an earlier year based on triggers raised from the assessors/PhV WP, informing the MS inspectorate concerned (i.e. where the EU QPPV is located). In this last case, for EU sites selected for these inspections, the MS concerned should inform EMEA whether or not the inspection of that MS site will be requested under their national programme or as CHMP request (the inspection of the 3rd country sites will normally be requested by the CHMP).

- Re-inspections will be determined by risk factors and will be focused on addressing critical findings observed in previous inspections, changes in the system or any product specific issues of concern for the assessors.

The preparation/revision of further four-yearly programmes will take place at least twice per year i.e. 1Q and 3Q 2008.

The programme should at least include the below details:

- MAH
- Brand name
- INN
- QPPV country
- Rapporteur country
- Co-Rapporteur country
- MS inspectorate proposed to lead the inspection (i.e where the EU QPPV is located or form the (Co-) Rapporteur country).
- Requestor of the inspection i.e MS or CHMP
- Scheduled year of the inspection

Additional details on inspection (e.g. inspected sites, dates of inspection etc) will be tracked in other working documents.

4.3 Adoption of the programme

This four-yearly programme should be agreed by the Ad Hoc PhV IWG and PhV WP and adopted by the CHMP the year before its implementation. As this programme will be a live document requiring periodic revision through the year, it is expected to be circulated for adoption at least twice, in the 2Q and 4 Q of the year.

The Ad Hoc PhV IWG will be provided with any adopted revised programme including a formal letter from the EMEA requesting that the inspections are performed.

4.4 Implementation of the programme

The nominated reporting inspectorate should ensure that these inspections take place as agreed and communicate to EMEA any change in order to amend the programme accordingly.

For those inspections conducted under the national programme, the reporting inspector should provide EMEA with the inspection reports (or a summary of the inspection report when the inspection report is written in the local language) whenever there are critical findings or substantial major findings, and information on how these substantial issues are being addressed is also provided.

For those inspections requested by the CHMP, the "Procedure for reporting PhV inspections requested by the CHMP" should be followed.

A flow diagram on the circulation of the inspection reports related to this programme is available in annex 4.

4.5 Re-inspections

The calculation of the next inspection date should result from the last inspection date and the risk assessment process. In principle a four year inspection cycle will be used but may be shortened or lengthened based on this risk assessment.

5 PROCEDURE SUMMARY

STEPS FOR THE PREPARATION OF THE 200X-200(X+3) EMEA PhV INSPECTIONS ROUTINE PROGRAMME

Steps	Sources	Responsibility	Timelines
1- Gathering information	SIAMED MS Inspectorates Other	EMEA IS	At least 1Q and 3Q 200(X-1)
2- Preparation and revision of the Programme 200X-200(X+3)	SIAMED MS Inspectorates Other	EMEA IS Ad Hoc PhV IWG PhV WP	At least 1Q and 3Q 200(X-1)
3- Adoption of the Programme 200X-200(X+3)		Ad Hoc PhV IWG PhV WP CHMP	At least 3Q and 4Q 200(X-1)
4- Implementation of the Programme 200X-200(X+3)		MS Inspectorates	200X-200(X+3)
5- Reinspections		MS Inspectorates	Four-year cycle unless considered to be performed later/earlier

ANNEX 1 FACTORS TO BE CONSIDERED WHEN DECIDING ON A ROUTINE PHV INSPECTION

Primary Prioritisation Factors

- The MAH was inspected (PhV inspection) and critical findings were identified;
- The MAH has a product with additional PhV or Risk Minimization/Management Activities;
- The MAH has never been inspected;
- The MAH has marketed product that received a commission decision at least 3 years ago;
- The MAH has the QPPV activity subcontracted or multiple licensing partners;
- The re-inspection date recommended by the inspectors as result of a previous inspection;

Secondary Prioritisation Factors (the following are examples of issues that can be secondary prioritisation factors):

- EMEA is aware that the MAH has recently been or is involved in a merger or takeover process;
- EMEA is aware that the MAH has changed their system significantly (e.g. new database system, contracting out of reporting activities);
- EMEA is aware that the MAH has the PhV activities subcontracted or has multiple licencing partners;
- Critical results of previous inspections (GCP, GMP, GLP);
- Adverse comments/safety concerns from agencies/bodies outside the EU;
- Non EU companies;
- The MAH PhV system has been designed only to address third country regulations;
- The MAH changed the QPPV since the last inspection;
- The MAH has many products in the market, covering many active ingredients;
- The MAH has only one CAP on the market;
- Size of the MAH (bigger company versus small);
- The absence of a Detailed Description of the PhV System (DDPS) e.g. products authorised prior to October 2005;
- Issues related to the DDPS;
- Product with large sales volume;

ANNEX 2 TRIGGERS TO BE CONSIDERED WHEN DECIDING ON A TARGETED PHV INSPECTION

- Delays in carrying out or failure to carry out specific obligations or follow-up measures relating to the monitoring of product safety, identified at the time of the marketing authorisation;
- Delays in expedited or periodic reporting;
- Incomplete reporting;
- Submission of poor quality or incomplete PSURs;
- Inconsistencies between reports and other information sources;
- Change in risk-benefit balance;
- Failure to communicate change in risk-benefit balance;
- Previous inspection experience;
- Information received from other authorities;
- Poor follow-up to requests for information from the Competent Authorities;
- Communication of information on PhV concerns to the general public without giving prior or simultaneous notification to the Competent Authorities or Agency as applicable;
- Product withdrawal with little or no advance notice to the EEA Competent Authorities;

ANNEX 3 TEMPLATE FOR COLLECTING INFORMATION ON PHARMACOVIGILANCE ISSUES FOR THE ATTENTION OF THE INSPECTORS/ASSESSORS

Template for collecting information on Pharmacovigilance issues for the attention of the inspectors/assessors

Reference number:	N° of pages: N° of attachments:	Date: *dd/mm/yy*

From: (*Member State/Agency*)

TO: *(obligatory)*

☐ EMEA INSPECTIONS SECTOR (gcp@emea.europa.eu)

(optional)

☐ Ad Hoc PhV IWG (forwarded by the EMEA)
☐ PhV WP (LIST-H-PHARMACOVIGILANCE@EUDRA.ORG)
☐ RAPPORTEUR (email)
☐ CORAPPORTEUR (email)
☐ OTHER, please specify:

PRODUCT/TRIAL/MAH:

Trade name(s):
INN:
Indication:
Procedure(s) of marketing authorisation (please select): CAP / MRP / DCP / national
Clinical trial title/number:
Post-marketing experience:
Other:

Marketing Authorisation Holder(s):
Sponsor of the clinical study:
CRO/3rd party:
Other, please specify:

INFORMATION: *(explain the issues and observations)*

REASONS FOR REPORTING THIS INFORMATION: *(summarise relevant evidence for concern and impact on other areas, NCAs, etc.*)

SOURCE OF INFORMATION: (*please select*)

- ☐ Preclinical data
- ☐ Authorisation assessment (pre- / post-)
- ☐ Inspection outcome/report
- ☐ MAH's communication with NCA/EMEA
- ☐ PSUR(s)
- ☐ Post-authorisation safety data/safety signals
- ☐ NCA, specify……..
- ☐ Other, specify……..

RECOMMENDED ACTION AND/OR ACTION ALREADY TAKEN:

- ☐ For information and/or discussion
- ☐ For use at the next inspection
- ☐ Triggered inspection should be scheduled
- ☐ Other, please specify:

ADDITIONAL INFORMATION: (*if applicable*)

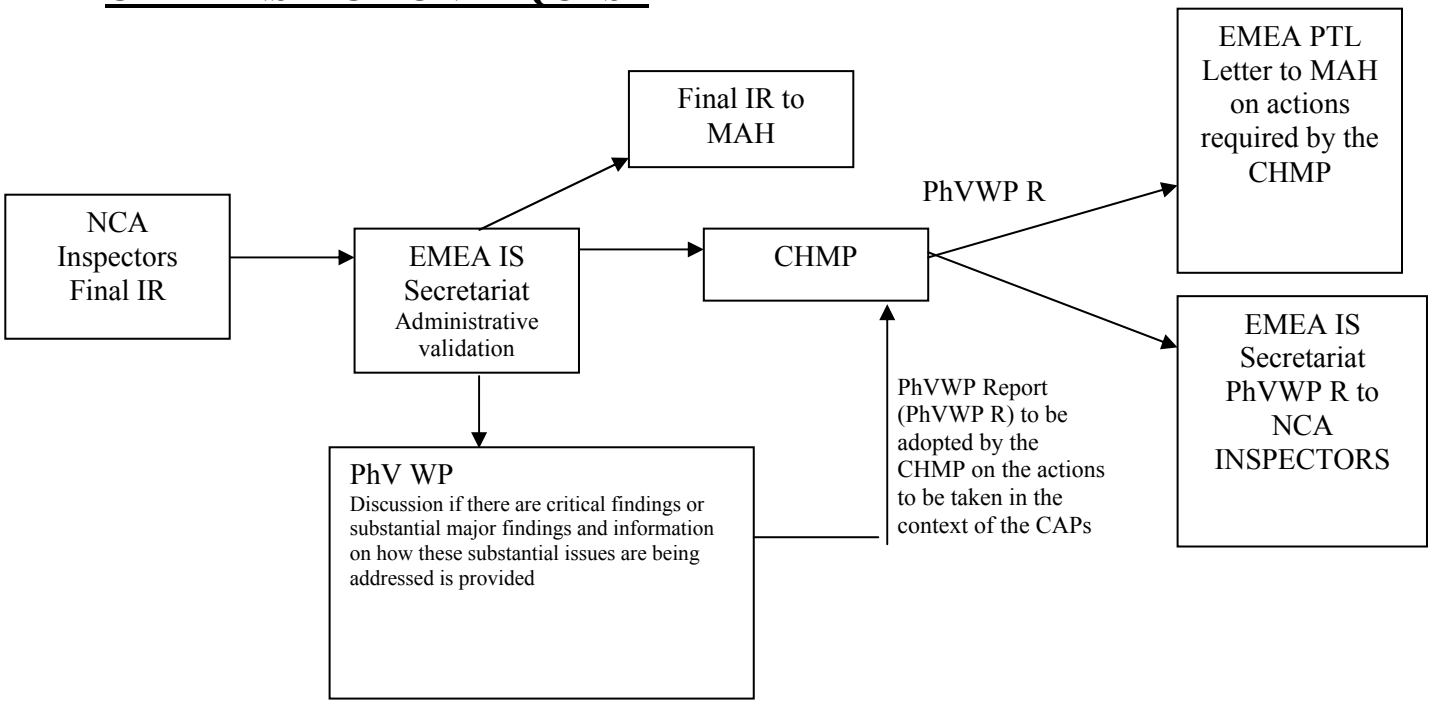
The issue could affect (an)other Member State(s): ☐ YES ☐ NO

INFORMATION REQUESTED: (*if applicable*)

NAME AND CONTACT DETAILS OF REPORTER:

ANNEX 4 CIRCULATION OF PHV INSPECTION REPORTS: FLOW DIAGRAM IN THE CONTEXT OF CAPS

CHMP INSPECTION REQUEST



NATIONAL INSPECTION REQUEST RELATED TO THE CAP PhV INSPECTION PROGRAMME